Respiratory System Compliance Measurements in the Care of Mechanically Ventilated Newborn Infants

Dr Benjamin J. Stenson

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Declaration

I declare that this thesis was written entirely by myself. The investigational work detailed within this thesis was performed collaboratively by myself, working in the Neonatal Unit of the Simpson Memorial Maternity Pavilion, Edinburgh and by my colleague Dr Rebecca Glover, working in the Neonatal Unit of Ninewells Hospital in Dundee. This collaboration enabled us to enrol a larger cohort of babies than would have been possible had we been working independently. Although we each gathered similar lung function and demographic data using the same methods, it was always our intent to consider different aspects of this data for our respective theses. As such the data, results and discussion presented herein are unique to this thesis and were prepared solely by myself. This thesis has not been submitted in candidature for any other degree, diploma or professional qualification.

Contents

Dedication

This thesis is dedicated to the infants studied and their parents who at a time of great personal stress were willing to participate in the research. Dr Ian Laing, Dr William Tarnow-Mordi and Dr Rosalie Wilkie provided invaluable guidance, support and friendship throughout the period of study, and without their encouragement it would not have been possible. I am indebted to the nursing and secretarial staff of the Simpson Memorial Maternity Pavilion. Their patience, understanding and assistance were essential. The studies were funded by the Scottish Office Home and Health Department.

Abstract

The success of neonatal intensive care in terms of morbidity and mortality is closely linked to the success of ventilator management. Although the ventilation of sick newborn infants has led to an increase in their survival it is clear that ventilation itself is associated with morbidity and mortality.

Ventilation requirements depend on the mechanics of the respiratory system. When the ventilator settings are inappropriate there is worsened gas exchange and a potential for unnecessary lung damage. The mechanics of the respiratory system change during the evolution of respiratory disease and therapeutic interventions such as surfactant replacement may cause more abrupt changes that necessitate adjustment of the ventilator settings.

Many new styles of ventilation are developing and with them techniques for measuring respiratory function and the interactions between infants and their ventilators. Studies suggest that these techniques may have the potential to improve infant care but they have not been systematically evaluated. The studies described in this thesis represent an attempt to determine the clinical value of routine measurements of static respiratory system compliance (Crs) using the single breath passive expiratory flow technique and their suitability for introduction into routine practice.

Measurements of Crs were found to be reproducible and safe but because of technical problems up to 20% of attempted measurements in unsedated ventilated infants were unsuccessful. Junior doctors were found to perform poorly at estimating Crs by inspection. They disagreed with one another as well as with the measurements. Many clinical circumstances were encountered where Crs data appeared to be useful.

Early improvements in Crs were seen following the treatment of respiratory distress syndrome (RDS) with a natural surfactant that were not seen when an artificial surfactant was administered. These changes may go some way towards explaining the mechanism of action of surfactant replacement therapy in human infants with RDS and the differences in clinical response observed between surfactant preparations. Crs measurements demonstrated some potential as a means of selecting infants for surfactant treatment. In a randomised controlled trial enrolling 245 infants regular measurements of Crs as an additional guide to ventilator management did not impact on the frequency of major adverse neonatal outcomes or reduce the duration of ventilator or oxygen dependence.

On the basis of these studies it may be concluded that although measurements of Crs using the single breath passive expiratory flow technique have a clear place in research they are probably unsuitable for introduction into routine practice. The real value of alternative methodologies should now be urgently evaluated as they are already being introduced into practice by equipment manufacturers.

List of abbreviations

a/A ratio	Arterial to alveolar oxygen tension ratio
BPD	Bronchopulmonary dysplasia
C/S	Caesarean section
C	Compliance
CLD	Chronic lung disease
Crs	Static compliance of the respiratory system
Crs_{an}	Analogue compliance
Crs_{op}	Optical compliance
CXR	Chest X-ray
EDD	Estimated date of delivery
FiO2	Fractional inspired oxygen concentration
FRC	Functional residual capacity
I	Inertance
IVH	Intraventricular haemorrhage
MAP	Mean airway pressure
ms	Milliseconds
PDA	Persistent ductus arteriosus
PEEP	Positive end expiratory pressure
PIE	Pulmonary interstitial emphysema
PIP	Peak inspiratory pressure
R	Resistance
RDS	Respiratory distress syndrome
Rrs	Respiratory system resistance
SBT	Single breath technique
sd	Standard deviation
s	Seconds
t	Time
TGV	Thoracic gas volume
$TcPCO_2$	Transcutaneous oxygen tension
$TcPO_2$	Transcutaneous carbon dioxide tension
USS	Cerebral ultrasound scan
VEI	Ventilator efficiency index
Δ	Change

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Chapter 1: Introduction and Methodology

Introduction

Technological advances over the last 20-30 years coupled with rapidly increasing medical expertise have led to huge improvements in our capacity to care for the seriously ill newborn infant. The neonatal mortality rate per 1000 live births in Scotland has fallen from 16 between the years 1961-70 to 4.5 in 1991 [1]. Undoubtedly many factors have contributed to these advances including better obstetric management, the treatment of sepsis with antibiotics, and an improved capacity to provide nutritional support to small infants. But perhaps the single most important development in practice has been the evolution of artificial ventilation. This has brought about the survival of many preterm infants who previously were felt to be non-viable as a result of inadequate development of their lungs.

Although there has been rapid progress in the mechanical ventilation of newborn infants in the last three decades, many of the concepts of neonatal ventilation are not new. In 1752 the Scottish obstetrician William Smellie described a silver endotracheal tube for the resuscitation of newborn infants and in 1776 John Hunter, a Scottish surgeon, had constructed a ventilator with a pressure limiting valve. In 1822 a Parisian, Leroy d'Etoilles, demonstrated that overinflation of the lung may cause pneumothorax. A monograph published in 1835 by Eduard Jörg entitled "Die Fötuslunge im gebornen Kinde" (Foetal lung in the baby who is born) was a description of the causes, complications and treatment of respiratory distress syndrome. The causes included immaturity, hypothermia and asphyxia.

The complications were right to left shunting, pneumothorax and pulmonary interstitial emphysema and the treatment, warmth, artificial ventilation (by mouth or instrument) and oxygen administration. He included a caution that high oxygen administration might cause inflammation of the lung. So by 1835 it was already becoming clear that excess inflation pressures and high concentrations of oxygen were damaging to the lung. Alexander Graham Bell in 1889[2] described an apparatus for ventilating newborn infants using negative extrathoracic pressures which failed to attract much interest. Ironically in the 1990's this technique is enjoying renewed interest[3]. By the 1950's interest in neonatal ventilation was widening[4] and by the 1960's it was becoming accepted.

Techniques of ventilation and equipment have changed considerably in a short time. Initial experiences were that the mortality of artificially ventilated infants was extremely high[5,6,7] but in the beginning only the sickest infants with little chance of survival were selected for treatment. Smythe et al[5] recognised in 1963 that many infants were dying of tetanus neonatorum because of mechanical ventilation with inadequate inflation pressures. They made this observation on the basis of measurements of arterial carbon dioxide tension and static respiratory system compliance. They found by monitoring static compliance during the course of the disease in a group of infants that problems with ventilation were explained by changes in the respiratory system compliance and that such problems could be overcome by adjustments in the pressures applied by the ventilator. Their new knowledge meant that they were sometimes raising the ventilator pressures under circumstances where they would previously have lowered them. They were able to dramatically increase the survival rate of their infants. As infants began to be ventilated for hyaline membrane disease the strategy for ventilation centred around mimicking the infants' spontaneous respiratory efforts, and ventilator rates of 60 to 80 breaths per minute were used.

In these critically ill infants with respiratory distress syndrome very high peak inspiratory pressures were often required to achieve adequate oxygenation and many of the treated infants died or developed bronchopulmonary dysplasia. As more experience was gained it was found that if the respiratory rate was lowered to around 30 breaths per minute and a longer inspiratory time was used that oxygenation could be achieved at a much lower peak airway pressure and inspired oxygen concentration [8]. The adoption of this approach was associated with an almost fivefold increase in the number of infants surviving ventilation [9]. These studies demonstrated very early in the modern history of infant ventilation that using a ventilation strategy appropriate to the particular underlying problem can have an important influence on clinical outcome.

As the success of mechanical ventilation has improved, the threshold for ventilation has become progressively lower and consequently the population characteristics of the infants being ventilated have changed. Smaller, less mature infants are now being ventilated [10] and some authors have suggested that a faster ventilator rate and shorter inspiratory time may be associated with a lower frequency of air leak or other complications [11,12]. Ramsden and Reynolds stressed the important point that it is unwise to make generalisations about the best way to ventilate an infant as the interaction between the respiratory system and the ventilator is highly dependent on the respiratory system mechanics at any given time [13]. Since these may vary considerably during the natural history of a particular illness [14,15, 16,17] there can be no single appropriate way to ventilate an infant. Perhaps the ideal would be to tailor the ventilator settings to the individual infants' instantaneous lung mechanics.

Although more infants now survive than before, it is often at the cost of chronic ventilator dependency and it may be that with further refinement of ventilation techniques morbidity and mortality could still improve.

The widespread introduction of antenatal steroids for mothers at risk of delivering preterm infants to promote foetal lung maturation and the use of surfactant therapy either as prophylaxis or rescue treatment for respiratory distress syndrome have great potential to influence infant survival and morbidity. Both of these treatments are undoubtedly highly effective [18,19,20] but their expanding use may not reduce neonatal unit workloads because they may the increase the number of ventilator dependent survivors. Recent estimates suggest that the mean duration of ventilation and hospitalisation of the smallest infants has actually been increasing [10,21]. These changes could have very important resource implications. The provision of neonatal intensive care is extremely expensive. The average daily cost of neonatal intensive care per patient in Birmingham (UK) in 1984 was £235 [22] (approximately twice the cost of care at lower levels of dependency). A similar estimate in Leeds (UK) in 1988 placed the cost at £467 [23]. The costs in 1995 must be higher still, particularly if the cost of surfactant treatment at around £500 - £1000 per infant are added. Any new treatment has to undergo economic as well as scientific scrutiny [24] and developments in care which could reduce costs are viewed with enthusiasm.

Every year mechanical ventilators offer a wider range of ventilation modes, each aimed at minimising the potential for lung damage and its consequences. There are many ways in which inappropriate ventilator settings might prove harmful to the infant. When excessive airway pressures are employed for a given degree of lung or respiratory system compliance, these pressures can be transmitted to the pulmonary and systemic circulations and have adverse effects on oxygenation, venous return and cardiac output [25,26,27]. If insufficient time is allowed for adequate expiration to occur between ventilator breaths, the resultant intrathoracic gas trapping can cause inadvertent positive end-expiratory pressure (PEEP) which may have similar effects on the circulation and worsen alveolar ventilation [13,28,29,30,31,32,33,34].

Under both of these circumstances the increased airway pressures may contribute to the already high risk of lung damage such as pneumothorax or in the longer term bronchopulmonary dysplasia [35,36].

The lung damage attributed to ventilation is often referred to as barotrauma, implying that it is caused by pressure. Neonatologists strive to minimise the ventilator pressures they use in the hope of avoiding it. Recent evidence suggests that it may be volume overdistension of the airspaces caused by pressure rather than the pressure itself that produces the damage [37,38,39,40]. Some now talk about volutrauma rather than barotrauma [41,42]. Pressure-controlled ventilation is the norm in neonatal intensive care and will probably remain so because it is easy to apply and monitor. There is a danger that by controlling pressures the importance of thinking about volume may be overlooked. Pneumothoraces have been associated with a high risk of death or serious brain damage from intraventricular haemorrhage [43,44]. Treatments like surfactant may have dramatic effects on the lung mechanics [45,46,47,48]. Under these circumstances prompt alterations to the ventilator settings may be required to maximise the potential benefits of treatment. If inadequate airway pressures are employed to maintain end-expiratory lung volume under circumstances where there is alveolar instability, alveolar ventilation and gas exchange may be sub-optimal [49,50,51,52] and the course of respiratory distress syndrome may be unnecessarily prolonged [53]. So ventilator settings that are either inappropriately aggressive or gentle could delay an infant's recovery, lengthen the duration of ventilator dependence and increase the risk of death, chronic lung disease or serious brain damage.

Successful outcomes in neonatal mechanical ventilation will depend on the caregivers having an appropriate knowledge of the underlying physiology and a wide experience of the effects of different strategies for ventilation in the clinical setting.

Clinicians judge an infant's ventilation requirements with the aid of visual assessments of lung inflation combined with auscultation findings and blood gas results, tailoring these to a knowledge of the natural history of the suspected underlying condition. Clinical assessments and the accuracy of clinical diagnoses are both subjective and may be liable to error particularly when made by less experienced individuals. There may be subconscious bias in favour of a diagnosis if this will allow the use of a popular therapy [54]. Respiratory diagnosis often depends heavily on the chest radiograph which can be similar in different conditions [55,56]. Junior doctors' estimates of chest inflation may not be as accurate as those of their seniors [57]. Their seniors may not be as accurate as they would imagine. A group of experienced senior anaesthetists manually ventilating infant test lungs with a variety of commonly used anaesthetic circuits were unable to detect when the endotracheal tube was completely occluded [58]. The blood gas results may not always help as they can be distorted by the ventilation strategy [27,30,59] The same gases may be obtained with different strategies that may be more or less damaging than one another. Although in most centres, highly experienced help is usually available, it is often less experienced junior doctors who provide much of the basic care. These problems increase the importance of finding other ways of supplying objective information about the clinical state to aid the decision making process. This has led to an interest in the potential utility of lung function measurements in this context.

It has been possible to make measurements of respiratory function on ventilated infants since the 1960's [5]. Perhaps because of the increased frailty of premature infants relative to older children or adults and limitations of equipment size, these methods have not found their way into routine clinical use. The ready availability of computerised methods has greatly simplified many measurement methodologies and the calculation of results, making tests rapid, well tolerated and easy to perform. At present they are largely confined to research centres.

Numerous studies have demonstrated the potential utilities of various methods of lung function testing in individual applications. Measurements of static respiratory system compliance (Crs) made in the neonatal period have been shown to provide a rapid estimate of early respiratory disease severity which correlates well with the risk of mortality [60]. A recent study suggested that Crs corrected for body length performed better as a predictor of disease severity than mean oxygen requirement in the first 12 hours of life and may be less liable to distortion by the ventilator settings [59] although the numbers of patients involved in the study were small. Mean FiO_2 in the first 12 hours of life has been shown to be at least as good a prognostic index as either birthweight or gestational age [61]. Compliance measurements have also been found to be a better predictor of death from respiratory distress syndrome than the disease severity suggested by the chest radiograph [62]. Measurements of Crs have shown promise as a rapid bedside method for determining biochemical lung maturity [63] and for predicting the likely success of extubation [64]. They have been less successful at predicting the development of chronic lung disease [65]. Although these studies have demonstrated that respiratory function measurements have the potential to improve clinical management they have not enrolled large numbers of infants, making it hard to assess whether they would truly impact on clinical outcome in some important way. There are no published randomised trials evaluating the potential of respiratory mechanics measurements to improve the outcome of neonatal care. The initial outlay for measurement equipment and investment of time spent developing the expertise to make and interpret the measurements mean that this is likely to be necessary before lung function testing finds its way into routine neonatal management. If any measurement of lung function is to be attractive to neonatologists as a potential clinical tool it will have to be applicable at the cot side to the smallest, sickest infants, be rapid, involve minimal handling of the infant, be reproducible and be easily learned.

Techniques for the measurement of lung volume either as functional residual capacity (FRC) or thoracic gas volume (TGV) have provided important information about the relationships of lung size to body size, the elastic and resistive properties of the lungs relative to lung size and the effect of various disease processes and ventilator strategies on lung volume [66,67,68,69,70,71,72,73,74]. These have greatly enhanced our understanding of the properties of the infant lung. Measurements of FRC or TGV are complicated and would be difficult to apply usefully in routine care at the present time although they may attract more interest with the increasing use of high frequency oscillatory ventilation. Adequate volume recruitment is central to the optimum use of this technique. This is currently assessed with frequent chest radiographs which necessitate considerable handling of the infant. Recent studies indicate that FRC measurements may aid optimisation of oscillatory settings [75] and that there is poor correlation between chest radiograph appearances and FRC [76,77].

Measurements of the compliance and resistance of the respiratory system or lungs have been the area of greatest interest in terms of clinical application. The most useful individual measure of lung function to a clinician will depend heavily on the nature of the clinical problems experienced with the particular patient group being cared for. The neonatologist ventilating mainly preterm infants many of whom will have reduced lung compliance as a result of surfactant deficiency is likely to be most interested in measurements of compliance. Those principally concerned with the care of mostly non-ventilated older infants, many of whom may have problems related to airway obstruction such as bronchopulmonary dysplasia, asthma or bronchiolitis, may be more interested in measurements of flow resistance. The studies presented in this thesis represent an evaluation of the potential utility and shortcomings of pulmonary function testing using the single breath technique as part of routine clinical management in neonatal intensive care. The principal study is a randomised controlled trial.

I have also considered the acute effects of surfactant treatment on the lung mechanics and the variation in these effects between a naturally derived surfactant and an artificial one. I have included an assessment of the ability of junior doctors to make clinical judgements of respiratory system compliance and an assessment of the inter- and intra-observer reproducibility of the technique. Finally some of the many cases of particular individual interest encountered during the course of these studies are described.

Methodology

The literature now contains many studies of infant lung mechanics which between them have used a plethora of techniques. Their results are difficult to compare directly because differing methods measure slightly different entities. No method of measurement is free of problems. The nature of the problems experienced depend in part on whether the measurements are made on intubated or non intubated infants. In intubated infants variations in airway resistance due to secretions may affect measurement results [16]. Also a large proportion of the total airway resistance is attributable to the endotracheal tube itself [78] and this varies with the calibre and length of the tube [79,80,81]. Air leaks around the endotracheal tube can result in inaccuracies in measurements of tidal volume. In non-intubated infants, variable laryngeal resistance can affect expiratory flow signals [82,83] and the increased respiratory dead space attributable to face mask apparatus can alter the respiratory pattern [84,85]. Difficulties also arise when comparison between ventilator and spontaneous breaths is attempted probably because different volume and pressure regions of the lung characteristics are examined [86,87,88].

Measurements of dynamic compliance have contributed greatly what is known about lung mechanics during infancy. This involves measuring the tidal volume between two points of zero flow during tidal exchange and dividing this volume by the change in pressure required to generate it [89]. The technique is applicable to both ventilated and non-ventilated infants. A number of problems have been identified with this technique, limiting its usefulness in ventilated preterm infants. Most studies have measured the dynamic compliance of the lungs rather than that of the whole respiratory system. This entails measuring changes in oesophageal pressure as a means of estimating the transpulmonary pressure. Oesophageal pressure changes have been demonstrated to be unreliable in small infants, particularly those with chest wall distortion during breathing [90,91,92,93]. They are increasingly unreliable when high airway pressures are in use [94]. This problem can be got over in ventilated infants by measuring the dynamic compliance of the total respiratory system as the tidal volume divided by the change in airway pressures measured at the endotracheal tube. Since the chest wall compliance is very high in the newborn [95,96,97,98,99,100], this would still give an estimate which predominantly reflected the properties of the lungs. But under dynamic conditions infants may maintain elevated intercostal muscle and diaphragmatic tone to defend their FRC [83,101] which could decrease the chest wall compliance, invalidating this assumption.

There are also problems of frequency dependence. Here the respiratory frequency and inspiration and expiration times can have important effects on the dynamic compliance results if inadequate time is allowed for all the volume changes that may occur with a given change in pressure to take place [102,103,104] This may occur under two circumstances. Firstly as described by Otis [105]. When the lung is composed of numerous alveolar units all with the same compliance and resistance then during ventilation they will all fill and empty at the same rate and a measurement of compliance will reflect the sum of their individual compliances.

If however the behaviour of the units is not homogeneous and there are many different local compliance and resistance values as may occur with lung disease, then some units will fill and empty faster than others. Under these circumstances as respiratory rate increases only the fast acting units fill and empty efficiently and the compliance may be seriously underestimated. Similarly even if the lungs are behaving homogeneously, if they are very compliant or the airway resistance is high, then the respiratory rate may be set so as to allow inadequate time for complete expiration. This would lead to intrathoracic gas trapping and a fall in tidal volume for a given set of pressures due to inadvertent PEEP, again underestimating the dynamic compliance.

When dynamic compliance is measured in ventilated infants there is usually positive end-expiratory pressure being employed. The dynamic compliance will be affected by the amount that the lung volume is elevated above true passive FRC by that end-pressure. If the lungs are very non-compliant then the PEEP may prevent alveolar collapse, keeping the lung in the optimal part of the pressure volume curve and result in improved compliance [34,50,51]. If on the other hand the lungs are compliant then the PEEP may result in alveolar overdistension, forcing tidal exchange to occur higher up the pressure-volume curve in its flatter portion where dynamic compliance would be decreased [106,107]. Changes in positive end-expiratory pressure of as little as 2cmH_2O can alter tidal volume by as much as 25% [49]. In ventilated newborn infants changes in PEEP may have twice the effect on tidal volume as the same change in peak inspiratory pressure [108]. Negative extrathoracic pressure has much the same effects as PEEP [109,110].

As a result of these problems dynamic compliance measurements may as much reflect the effects of ventilatory pattern on the respiratory system as truly measure its underlying physical characteristics.

Whilst this may mean that individual dynamic compliance values can be hard to interpret in relation to those of other infants, the method may still supply very useful information in the management of individual infants by helping to determine the most efficient style of ventilation. By selecting the ventilator settings associated with the optimal dynamic compliance, both over- and under-inflation of the lungs could be avoided, thereby reducing barotrauma and this might result in improved clinical outcome [111]. This hypothesis is not yet adequately proven. For the time being, the true usefulness of dynamic compliance measurements in routine clinical management is questionable and studies performed on ventilated infants which utilised oesophageal pressure measurements as part of their methodology should be interpreted with caution.

An alternative to dynamic techniques is to measure the total respiratory system mechanics under static conditions. This removes the problems of frequency dependence and oesophageal pressure measurements. The term static implies that the measurements are made at points of zero flow when adequate time has been allowed for equilibration of volume and pressure throughout the respiratory system. Static compliance measurements were initially of limited clinical use as they were only possible in heavily anaesthetised or paralysed subjects. This is because spontaneous respiratory efforts must be inhibited for sufficient time to allow the airway pressure and volume changes to become truly static. This problem has been overcome by the development of airway occlusion techniques which employ the Hering-Breuer reflex [112] to inhibit respiratory activity.

The method of measurement selected for these studies was the single breath passive expiratory flow technique which enables simultaneous estimation of the static compliance, the resistance and the time constant of the respiratory system.

The use of this method in human infants was first described in 1984 by LeSoeuf and colleagues [113] and it has now been employed by a large number of authors [14,15,114,115,116,117,118]. The method gradually evolved through experimental work derived from the equation of motion of the respiratory system as proposed by Rohrer.

$$P_L = -(Pel + Pres + Pin) \quad (1)$$

This equation states that any pressure applied to the respiratory system by the respiratory muscles (P_L) will be equal and opposite to the opposing pressures developed within the system. These opposing pressures are the sum of the pressures arising as a result of the elastic (P_{el}), resistive (P_{res}) and inertial (P_{in}) properties of the components of the system. Compliance (C) is the elastic property, resistance (R) the resistive property, and inertance (I) the inertial property. They are defined as:

$$C = \frac{V}{Pel} \qquad R = \frac{Pres}{\dot{V}} \qquad I = \frac{Pin}{\ddot{V}}$$

where V is the incremental volume change of the respiratory system, $\dot{V}$ is the gas flow rate and $\ddot{V}$ is the volume acceleration of the respiratory system. The inertial component was left out in the following experiments that were derived from the equation of motion of the respiratory system and formed the basis of the single breath technique as in practice it was found to be negligible in comparison to the other forces involved [119,120,121,122].

In 1954 Comroe et al first used the properties of relaxed expiration to determine the resistance of the respiratory system in cats and dogs [123]. They achieved respiratory muscle relaxation through anaesthesia, paralysis, hyperventilation, or the use of the Hering-Breuer reflex.

Expiratory volume was plotted against time during relaxed expiration, and the flow at any given point was determined by the slope of the tangent to the volume-time graph. The pressure driving this flow was taken from the static pressure-volume relationship for the lung at the same expired volume as that at which the flow had been calculated and these two values were used to determine the resistance as pressure divided by flow. Brody [119], by mathematically manipulating the equation of motion, found that passive expiratory flow should occur exponentially as long as the resistance due to turbulent flow is minimal. He analysed passive expirations in dogs and humans and found that they occurred exponentially in dogs when turbulence was minimal but not when flows were high and that attempts at passive expiration made by adult human subjects were not truly passive. He suggested that they were affected by inspiratory muscle tone during expiration. McIlroy et al [124] extended the technique. Starting with equation (1), accepting that the inertance component of the respiratory system behaviour is negligible then:

$$P_L = -(Pel + Pres)$$

or rearranging this

$$P_L + Pel + Pres = 0 \quad (2)$$

The pressure applied to the respiratory system by the respiratory muscles now equals the opposing pressures due to the elastic recoil and frictional resistance of the lungs and thorax. During a truly passive expiration the pressure applied by the respiratory muscles would be zero and all the pressure overcoming resistance would be derived from the elastic recoil.

$$Pres = -Pel \quad (3)$$

Since Resistance (R) and compliance (C) are defined as:

$$R = \frac{Pres}{\dot{V}} \qquad C = \frac{V}{Pel}$$

If the resistance and compliance of the respiratory system are constant then equation (3) can be solved as:

$$\frac{V}{\dot{V}} = -RC \text{.....(4)}$$

Therefore as long as the resistance and compliance are constant, the instantaneous ratio between the expired volume and rate of airflow during a relaxed expiration should be constant and equal to the product of the resistance and compliance of the system. On this basis McIlroy et al [124] reasoned that the finding of a straight line relationship between flow and volume during expiration should imply that the subject had managed to relax completely his/her respiratory muscles. The alternative, less likely explanation would be that resistance and compliance had changed by exactly equal and opposite proportions. They found that most subjects could be trained to expire passively with a linear flow-volume relationship and that if an added resistance were placed in the circuit the relationship remained linear. This would not be the case if the compliance and resistance of the respiratory system were changing by equal and opposite amounts whilst the added resistance remained constant. So they concluded that the ratio of flow and volume was constant during a passive expiration indicating that the relaxed respiratory system empties exponentially. They used paired measurements made with and without an added resistance in series to calculate the changes in the slope of the flow-volume relationship and calculated the compliance and resistance of the respiratory system by solving equation (4) and an extension of equation (4) incorporating the added known resistance.

They found the method to produce reproducible results for compliance and resistance and for the value of the added resistance in both a lung model and in human subjects.

On the basis of these findings, Bergman [125] suggested that these exponential characteristics of passive exhalation described by Brody and McIlroy might be utilised to measure resistance without the need to measure gas flow. Since flow rate ($\dot{V}$) is change of volume per unit change of time:

$$\dot{V} = \frac{dV}{dt} \quad \text{.....(5)}$$

By substituting this into equation (4) and rearranging it the following is derived:

$$\frac{1}{V} dV = -\frac{1}{RC} dt \quad \text{.....(6)}$$

If this equation is integrated an exponential equation is obtained.

$$V = Voe^{-(1/RC)t} \quad \text{.....(7)}$$

where V is the volume of gas in the thorax t seconds after the start of expiration, V_o is the total expired volume at the end of the breath and e is the base of natural logarithms. RC is the time constant of this equation such that after a time t of RC seconds the volume (V) of gas remaining in the thorax is now:

$$V = Voe^{-1} = Vo \times 0.368 \quad \text{.....(8)}$$

Bergman reasoned that if the equations were applicable, the value of RC for a passive expiration could be determined from the time taken for the volume of gas remaining in the lungs to reach 0.368 of its original value using the resting end-expiratory level as the zero reference level. By then measuring the static compliance (C) the resistance (R) could be determined from the value of RC. He studied anaesthetised, paralysed adults measuring static compliance as the volume exhaled passively following release of a sustained inflation divided by the transthoracic pressure recorded during the sustained inflation. He then determined the time constant as the time taken for the thoracic volume to decrease to 36.8% of its end-inspiratory value and calculated the resistance from these two values. His results showed that the ratio of volume to flow is constant throughout the greatest part of passive expiration in paralysed subjects, confirming the exponential nature of passive expiration. In addition the slope of the flow-volume relationship was numerically equal to the time taken to exhale to 36.8% of the end-inspiratory volume establishing the validity of the equations. The resistance values calculated using the time constant were not significantly different from those measured by the simultaneous measurement of transthoracic pressure and gas flow, further validating the technique. The methodology still depended on muscular paralysis or training conscious subjects in the technique and was thus not applicable to young children or infants.

In 1976 Olinsky et al [126] devised a simple method of measuring the static respiratory system compliance that was applicable to newborn infants and did not require paralysis or anaesthesia because respiratory muscle inactivation was achieved by provoking a Hering-Breuer reflex. This reflex was first demonstrated in human infants by Cross et al in 1960 [127]. They showed that term infants responded to lung inflation with an apnoeic pause. This pause got longer with increasing inflation volumes but appeared to diminish with age suggesting that it may not be present after about 8 days of age.

Olinsky et al also demonstrated the Hering-Breuer reflex in newborn infants [128]. They went on to measure the static respiratory system compliance, utilising the Hering-Breuer reflex, by occluding an infant's airway at different volumes above the resting end-expiratory volume and measuring the airway pressure generated by the recoil of the respiratory system during the resultant apnoeic pause. This pressure is assumed to equal the alveolar pressure as long as sufficient time has elapsed for all volume and pressure redistributions within the respiratory system to occur. By repeating this manoeuvre at a number of different volumes a graph was plotted describing the volume-pressure relationship within the range of tidal respiration. This relationship was linear and the static compliance of the respiratory system was the slope of the line calculated by regression. They also measured dynamic lung compliance in the same infants and found that it was consistently less than static respiratory system compliance. The difference between the two increased with increasing respiratory frequency, suggesting that dynamic compliance measurements in normal infants were frequency dependent. A further interesting finding was that extrapolation of the volume-pressure graph to the volume axis gave a negative intercept suggesting that the infants were breathing above a dynamically elevated end-expiratory lung volume rather than the passive functional residual capacity that would be determined by the static balance of forces between the lung and chest wall, a finding now established by many studies [129,130,131,132,133].

Mortola et al [134] used the Hering-Breuer reflex to achieve respiratory muscle relaxation in another series of infants and as well as measuring the static compliance by the Olinsky technique plotted passive expiratory flow against volume. They determined the time constant RC as the slope of the expiratory flow-volume relationship and were thus able to calculate the respiratory system resistance. They again found that the expiratory flow-volume plot was predominantly linear.

At about the same time Zin et al [135] making measurements on intubated cats measured the static compliance, resistance and time constant of the respiratory system using a single breath. At end inspiration the airway was occluded, inducing a Hering-Breuer reflex. The airway pressure was measured once it had reached a plateau. The animal was then allowed to exhale passively to atmospheric pressure during which time the flow-volume relations of the complete expiration were plotted. Static compliance was the expired volume divided by the plateau pressure. The slope of the flow-volume plot was the time constant and this was used to determine the resistance. In the same paper they reported their finding in a similar experiment that during the induced apnoeic pause there was no measurable phrenic nerve activity either during the pressure plateau or the subsequent relaxed expiration showing that the diaphragm was relaxed as well as the intercostal muscles. They were able to obtain reproducible results with and without added resistive loads indicating that compliance and resistance were linear within the experimental range of flows and volumes.

Le Souef et al [113] applied this method to newborn infants but extended it, making it applicable both to normal infants and to those with severe respiratory illness. They identified that one of the problems with measuring passive expiratory volumes in newborn infants, particularly those with respiratory disease, is that they defend their FRC by breathing in again before expiration is complete. They solved this problem by extrapolation of the linear portion of the flow-volume plot to the axis giving the volume that would have been expired to FRC were it not for early inspiration. By subtraction of the actual expired volume they were able to calculate the volume by which FRC was being dynamically elevated by the infant. They observed linear flow-volume relationships in both spontaneously breathing and ventilated infants.

They also made calculations of the expiratory flow rates required to generate turbulent gas flow for the range of endotracheal tube sizes which they used and found that in most instances the flow rates in the study did not exceed these and that even when they did, the departure of the flow-volume relationship from linearity was minimal indicating that endotracheal tube turbulence was not making an important contribution to respiratory system resistance. Their method had the advantage over the Olinsky technique that fewer breaths needed to be sampled and that information about the resistance and time constant was also obtained. Nevertheless static compliance values from both methods are determined by similar means and it is not surprising that they have been found to be similar [114,118,136,137,138] and it has been suggested that where there is doubt about the validity of the results obtained with one method it may be checked using the other [118,138]. It has been suggested that the Olinsky technique might be used in favour of the single breath technique in non-intubated infants as laryngeal modulation of expiratory flow would not be inhibited by the Hering-Breuer reflex [139]. The increased resistance due to laryngeal braking could lead to overestimation of compliance results through extrapolation of the flow-volume relationship to a falsely elevated expired volume with the single breath technique . Although this suggestion is not supported by the findings of studies where constant external resistive loads were added and compliance results remained reliable [124,135,137] Crs results were found to be overestimated by the single breath technique when the difference between the actual expired volume and the volume intercept of the linear portion of the flow-volume trace was large [118,138]. Variable expiratory resistance would invalidate single breath measurements by making the flow-volume relationship non-linear. Obviously, any laryngeal braking would make resistance measurements unreliable.

From the above discussion it is clear that the validity of results obtained using the single breath technique depends on the accuracy of a number of assumptions under the circumstances where a measurement is made. If these conditions are not fulfilled then the results may be inaccurate or potentially misleading.

(A) The respiratory system is behaving as a single compartment model with a single compliance and resistance

(B) All the respiratory muscles are relaxed during the airway occlusion and the subsequent relaxed expiration.

(C) The respiratory system inertance is negligible under the measurement conditions.

(D) All pressures and flows within the system have truly equilibrated at the point that the occlusion pressure is measured.

Single compartment model

It may be reasonable to assume that the respiratory system behaves as a single compartment in health as suggested by the above data but this is not always the case when there is lung disease. Variations in resistance or compliance during the respiratory cycle would make the flow-volume relationship non-linear as would the existence of inhomogeneities within the lung resulting in a mixture of compartments with differing time constants [140,141]. This would make it impossible to assign a single value to the time constant, resistance, and compliance. This is often seen to be the case in infants with chronic lung disease where the flow-volume relationship is found to be curvilinear and limits the number of infants with chronic lung disease that can be successfully measured with the single breath technique.

As a result of this there has been interest shown in using more complex mathematical models to describe and interpret the respiratory system behaviour under these conditions [140,141,142]. These may be valid but their complexity has limited their popularity and clinical application so far. This is one circumstance where the Olinsky technique would be more useful for measuring the compliance as it does not depend on a linear flow-volume relationship. As this thesis examines the utility of single breath measurements alone, in some instances where there was alinearity of the flow-volume trace respiratory function data was not obtainable.

Respiratory muscle relaxation

It is assumed that the respiratory muscles of human infants are relaxed by the Hering-Breuer reflex during the airway occlusion and the subsequent passive expiration. Animal studies have demonstrated that both the intercostal muscles and the diaphragm are inhibited by the Hering-Breuer reflex [135,143,144]. It has been shown by many studies that human infants (including preterm infants) have a readily elicitable Hering-Breuer reflex [127,128] that persists beyond the neonatal period [145,146,147]. Of particular relevance to the use of lung mechanics measurements in ventilated neonates are the observations that the reflex is easier to elicit in preterm infants than term infants [148,149] and in those with reduced lung compliance [150] and its intensity is not reduced by sedation [146]. Conversely Gerhardt et al found it to be weaker in premature infants in a small series [151]. Absolute exclusion of muscular activity during the reflex would require this to be measured simultaneously which has not been studied directly in humans and is an area where further research would help to validate the technique fully. There are however human studies which strongly support the assumption. Using the multiple occlusion technique, Fletcher et al [152] measured Crs before and after pharmacological muscular paralysis and noted no change in the results when measurements were made at similar tidal volumes to those prior to paralysis.

Shulman et al [153] noted no change in the expiratory time constant measured using the single breath technique before and after pharmacological paralysis. When measurements are made, muscle relaxation is assumed if there is a satisfactory pressure plateau following airway occlusion and a linear flow-volume relationship. Both of these could still be seen if there were a constant level of muscular activity throughout these phases. The likelihood of respiratory muscle activity distorting the measurement can be reduced by calculating the result of any study from at least several satisfactory breaths as any muscular activity would be very unlikely to remain constant under these circumstances. The effect of any muscular activity would be minimised by taking the average of all the satisfactory breaths. Since changes in muscle activity would change the chest wall compliance, the respiratory system compliance and the time constant, inaccuracies can be further limited if only those studies in which the variation between breaths is minimal are accepted. The flow-volume trace can often be affected by muscular activity in its terminal portion as infants may inspire before end-expiration or actively expire once the Hering-Breuer reflex has worn off [113,138,154] so it is advisable to avoid using the most terminal parts of the flow-volume trace for calculation. Obviously these problems do not occur when the technique is applied to paralysed infants.

Inertance

As described above, inertance has been measured by a number of authors and the assumption that it is negligible under the conditions of conventional mechanical ventilation in infants would seem reasonable in most circumstances. Under truly static conditions there is no acceleration taking place and therefore inertial properties are not important.

Equilibration

The assumption that all changes in flow and pressure have reached equilibrium is crucial to the term static compliance. Equilibration may be said to have occurred once there is a clearly defined pressure plateau in the airway pressure trace following airway occlusion. If the occlusion is released before equilibration has taken place compliance may be over- or underestimated. Since equilibration depends on the time taken for flow and pressure changes to occur within the lungs, the time taken for equilibration will depend at least in part on the compliance and resistance. Infants with very stiff lungs and low airway resistance should reach equilibration more quickly than those with relatively normal compliance and high airway resistance. It has been shown that the results of single breath measurements made on infants with bronchiolitis vary with the length of time that the airway is occluded until occlusion times of $\geq$ 275 milliseconds (ms) are used [117] but in that study occlusion was automated and pressure traces were not examined for a satisfactory plateau. It is important to distinguish between airway occlusion time and pressure plateau duration as different authors refer to one or the other. Small infants with RDS may have reached equilibrium after a plateau duration of $\leq$ 100 ms [155]. There is no established standard. Different authors have used occlusion times/pressure plateau durations varying from 50 ms to 500 ms [136,154,156,157]. The interrupter technique is a variation of the multiple occlusion technique whereby, using an automated system, multiple airway occlusions are performed during expiration and the airway pressures measured during these occlusions are plotted against the expiratory volume to generate a pressure-volume relationship [138,142,158]. In these studies occlusion times of 50-80 ms were used and, whilst the automation of this technique may make it simple to apply, until a lot more data is available to validate results obtained using such short equilibration times, they should be interpreted with caution. Other authors have used this technique with longer occlusion times but the infants concerned were either heavily sedated or paralysed [159].

As well as defining the duration of the airway pressure plateau some authors have defined the plateau mathematically [118,138,154,160] in terms of the acceptable deviation from the mean plateau pressure over a given time. These criteria can be applied if data is analysed by computer. Using a long plateau time can also be problematic as the Hering-Breuer reflex may wear off during expiration allowing active inspiration or expiration to distort the flow-volume trace. The ideal time is likely to vary between infants.

As with all methods, when the single breath technique is used there must be careful quality control to ensure the validity of the results. It must be recognised that no one value for compliance will truly describe the mechanical properties of the lungs. The static relationship of pressure and volume of the respiratory system is sigmoid in shape rather than linear [161,162]. Relatively high pressures are required to produce a given change in volume as a collapsed lung begins to inflate. There then follows a relatively linear portion through which the compliance is better. At higher lung volumes the relationship flattens again as greater pressures are required to generate a given change in volume. Tidal ventilation usually takes place in the linear portion of the curve where compliance is relatively constant [161,162] but measurements made at different lung volumes or pressures may produce varying results in the same lungs [87,88] so results should be expressed in relation to the pressures or volumes at which they were made. For reliable comparison, successive studies made in the same infant should be made at similar pressures or volumes [152,163]. In normal clinical management ventilator settings are adjusted according to the apparent needs of the individual patient so it would be impracticable for all studies to be conducted at the same ventilator settings. In most cases tidal volume remains within a relatively narrow range as ventilation is adjusted in response to changes in lung function and comparison of successive studies is feasible.

Respiratory system compliance results can vary with posture and this should be standardised if studies are to be compared [164,165,166,167,168,169]. In intubated infants the accumulation of secretions in the endotracheal tube can cause large inaccuracies in measurements of resistance [16], so endotracheal suction shortly before lung mechanics measurements is advisable. Airway suctioning may lead to a temporary loss of lung recruitment, causing a temporary fall in lung compliance as a consequence so studies should not be performed too soon afterwards. Likewise prolonged or large inflations may temporarily recruit lung volume allowing compliance to be overestimated [152]. Studies should therefore be performed in the context of a similar lung volume history. Any air leak from the system can lead to inaccuracies in measurements. In practice these tend to occur when pressure is maximal during airway occlusion. Significant leak would prevent the establishment of a pressure plateau. This is another important reason for checking for the presence of an acceptable plateau. In practice air leaks can usually be overcome by gentle fingertip pressure over the trachea but some studies are invalidated when this is not successful [155].

Expression of data in relation to infant size

For lung function data to be useful to the clinician it must be presented in a form which allows some comparison of an individual result to what it might be expected to be were the lung function normal. A crucial aspect of this about which there is no consensus is the expression of results of compliance or resistance measurements in relation to the size of the infant concerned. Neonatologists tend to correct compliance measurements for body weight, Physiologists for FRC and Paediatricians and Respiratory Physicians for height (or length). None is consistently ideal. The solution to the problem will depend on the reason that lung function is being measured and the age group of the population being studied.

In normal individuals throughout life, the compliance of the lung is directly proportional its size or volume and the relationship passes very close to the origin [66,67,70,71,73,170,171]. This has led many to believe that compliance values should be corrected to FRC and expressed as specific compliance. There are a number of problems with this approach. Obviously to correct compliance measurements to FRC in clinical practice would require that both were measured. Compliance and FRC are inextricably linked. Reduced FRC implies there are fewer recruited alveoli available for expansion by applied airway pressure. Reduced compliance increases the tendency for alveoli to collapse at end expiration which reduces FRC. In clinical practice one is usually dealing with the abnormal rather than the normal. Many newborn infants with respiratory disease particularly those with surfactant deficiency will have reduced FRC as a component of the problem [74,172,173]. Partly as a result of this but also because of increased surface tension throughout their respiratory cycle these infants will have reduced compliance. Expressing their compliance results corrected to FRC would underestimate their compliance abnormality and decrease the clinical usefulness of compliance data. A clearer example of this would be a ventilated infant who is intubated with an endotracheal tube which passes into the right main bronchus forming a snug fit. If compliance and FRC were now measured the infant would have a compliance that was roughly 50% of normal but the specific compliance would be approximately normal. The infant would require a substantial increase in ventilator settings reflecting the reduced compliance until the problem was remedied.

Many newborn infants maintain their FRC substantially above the position determined by the balance of the passive forces in the respiratory system by a number of mechanisms such as post-inspiratory activity of the diaphragm and intercostal muscles, laryngeal braking of expiration, and early inspiration before expiration is complete [82,126,129,130,131,132,174].

These factors may vary considerably with sleep state [101,130,133] although this has not been a universal finding [175,176]. Lung volume changes over the first hours of life with the absorption of the foetal lung fluid and varies in early life according to the mode of delivery [177] and so measurement of FRC may reflect other dynamic factors as well as the properties of the lungs. This is particularly important in the case of ventilated infants in whom there is almost always positive end expiratory pressure (PEEP) being applied as part of the management strategy. As discussed above, PEEP will elevate FRC by an amount determined by the level of PEEP and the static compliance. Indeed this is the basis of the weighted spirometer method for measuring static compliance [171,178]. Small changes in PEEP can cause large changes in FRC [25,34,106,179]. FRC measurements are also frequency dependent [28,180]. Improvements in compliance would increase the amount that the lung volume was being elevated above passive FRC by PEEP and would therefore be masked if they were expressed as specific compliance. Measurements of FRC are technically difficult, particularly in ventilated preterm infants and would be difficult to make serially as a routine index of lung function. All of these factors limit the value of expressing compliance corrected to measured FRC in ventilated infants with lung disease and it has been suggested that measurements may be better corrected to some index of predicted FRC [181].

Predictions of FRC may be based on body length or body weight. In preterm infants both of these are oversimplifications because the rates of growth of different tissues of the body are non-uniform [66,69,70]. At different stages of development, the ratio of lung volume to body weight or body length varies. Most authors have found that lung volume is linearly related to body weight. However when one is plotted against the other the intercept is on the volume axis. This means that larger infants have a lower lung volume per unit body weight than smaller infants [66,68,69,70,182,183]. Consequently, correction of compliance values to body weight would tend to overestimate slightly the disease severity of heavier infants and underestimate that of lighter infants.

Weight is relatively easy to measure accurately but can vary by more than 10% in an individual infant over the first few days of life and the degree of adiposity can vary significantly in relation to nutrition in late gestation. The relationship of FRC to body length has been found to be linear by some authors [66,71,72,171] and curvilinear by others [69,170]. The intercept of the relationship of FRC and body length is on the length axis. This means that correction of compliance values to body length would tend to overestimate the disease severity of smaller infants and underestimate the disease severity of larger infants. Length is more difficult to measure accurately but does not vary significantly in the short term. These observations about the relationship of FRC to body size are supported by compliance studies. Crs in neonates has been found to be linearly related to weight with an intercept on the Crs axis [114,156,184,185] and both linearly [114,126,171,185] and cuvilinearly [69,157,170,184,186] related to length with an intercept on the length axis.

The optimum method of correcting lung function tests for size in the clinical setting is that which yields the most useful information. The most important cause of respiratory problems in neonatal intensive care is surfactant deficiency which is more likely to occur the smaller or less mature the infant. The risk of death from respiratory disease in the neonatal population increases with decreasing birth weight. On this basis, it might be expected that an index of disease severity with a degree of bias toward smaller infants might be found to be more clinically useful than one with a bias toward larger infants. Few authors have directly compared the usefulness of different methods of correcting lung function data for infant size. Tarnow-Mordi et al found correction of compliance measurements to body length to be a better predictor of death from respiratory distress syndrome than correction to body weight [59]. Wilkie et al found that compliance corrected to length was a better predictor of biochemical lung immaturity than compliance corrected to weight [63].

On this basis the compliance measurements made in the studies described in this thesis were corrected to body length. These observations may not apply outside the neonatal period when prognosis is less critically dependent on infant size and in any clinical study careful consideration should be given to this issue.

Reference values

Many authors have reported respiratory system compliance data obtained from normal infants. Most of the data series are small. There is no consistency in the way the results are expressed. Some authors have provided regression equations describing the relationship between compliance and various indices of body size for their study populations whereas others have given the mean and standard deviation for the whole study population assuming that all the infants in the age range studied have a similar ratio of compliance to whatever index of body size it is corrected to. Different series considered infants of different degrees of maturity and size and also of differing postnatal ages. This makes the data difficult to summarise. From the discussion above about correction of results for body size it is obvious that expressing the results per unit body size is a simplification but using regression equations to compare individual results to normal would be cumbersome in routine clinical use. Therefore where possible the reference data described below is expressed as the population mean per unit of body size. This approach is reasonable as long as the range of infant sizes considered is not too wide. Where regression equations were supplied rather than individual data points they have been used to calculate the expected compliance per unit body size of a 1kg and a 3.5kg infant or a 35cm and a 50 cm infant.

Since the study population considered in this thesis consists exclusively of ventilated neonates, most of whom are preterm, the studies selected as representing normal data are all those found in the literature measuring static respiratory system compliance by the single breath technique or any method reasonably comparable to it in infants, term or preterm measured less than one month beyond their expected date of delivery (EDD). Normal values for term and preterm infants breathing spontaneously who were free of respiratory problems are summarised in table 1.1 Values for infants requiring ventilation for respiratory distress syndrome are summarised in table 1.2. The study by Olinsky et al [126] was included in table 1.1 as, even though some of the infants must have been a little older than one month past their estimated date of delivery, the range of body weights and lengths of the infants studied was similar to those of the other studies. The study by Thomson et al [184] was included in table 1.1 after excluding the results from the older infants. Measurements of dynamic compliance are not considered because of the important differences between dynamic and static measurements already discussed.

Whilst normal data may give some basis for comparison they are not likely to be very informative when lung function tests are used to aid the management of ventilated infants. Normal infants have a considerable respiratory reserve which has to be exhausted before they will need to be ventilated. Similarly the lung function of ventilated infants does not have to return to normal before extubation will be successful. Extubation is usually successful with respiratory system compliance values that are approximately 50% of normal [64] and this level of "functional normality" in terms of the requirement for ventilation may be a more relevant baseline than absolute normality.

Table 1.1: Reference values for static respiratory system compliance (Crs) in normal spontaneously breathing newborn infants. Data are ranges or mean ± SD unless stated otherwise.

First author	Method	No. of infants	Gestational age (weeks).	Age at study	Weight (kg)	Length (cm)	Crs (ml/cmH_2O)	Crs ($ml/cmH_2O/kg$)	Crs ($ml/cmH_2O/m$)
Olinsky [126]	MOT	12	NG	1 day - 30 weeks	1.13 - 4.55	38.5 - 56.5	3.73 ± 1.49	1.53 ± 0.316	7.83 ± 2.36
Taeusch [187]	MOT	10	38 - 43	4-6 days	2.6 - 4.5	45 - 53	3.47 ± 0.47	1.03 ± 0.27	6.98 ± 1.53
Simbruner [60]	SBT	52	30 - 41	45 - 475 min	1.33 - 4.35	NG	2.07 ± 0.48	0.76*	NG
Mortola [134]	MOT	10	"Term"	1-5 days	3.41 ± 0.49	NG	3.679 ± 0.49	1.07*	NG
Mortola [83]	SBT	12	"Term"	1-4 days	3.38 ± 0.31	NG	NG	1.12 ± 0.3 (SD)	NG
Tepper [178]	WST	10	"Term"	1 - 2 days	2.9 - 3.8	49 - 55	3.7 ± 0.5	1.11 ± 0.16	7.3 ± 1.1
Thomson [184]	MOT	28	26 - 40	0 - 9 weeks	0.94 - 3.5	35 - 51	2.16 ± 0.86 §	1.16 ± 0.26 §	4.88 ± 1.5 §
Migdal [156]	MOT	20	37 - 41	1-28 days	2.6 - 3.715	46 - 54	3.17 ± 0.71	1.0 ± 0.22	6.4*
Migdal [156]	MOT	19	31 - 36	1-29 days	1.38 - 2.9	40 - 48.5	2.37 ± 0.81	1.11 ± 0.32	5.3*
Popow [185]	EIOT	78	28 - 41	45 - 480 mins	0.830 - 4.35	33 - 52	2.4 (if 3.5 kg)	0.7 (if 3.5 kg) † 1.4 (if 1kg) †	4.6 (if 50cm) † 3.3 (if 35cm) †
Haouzi [114]	SBT/MOT	24	26 -40	2 - 29 days	1.26 - 3.98	41 - 53	2.5 ± 0.568	1.15 ± 0.29	5.53 ± 1.03
Gappa [118]	SBT	24	29 - 35	1 - 14 days	1.07 - 2.68	41.2 - 48.2	2.87 ± 0.585	1.548 ± 0.272	6.507 ± 1.257

MOT = multiple occlusion technique, SBT = single breath technique, WST = weighted spirometer technique, EIOT = end inspiratory occlusion technique, NG = data not supplied by authors, * = calculated from data supplied by dividing mean Crs by mean unit of body size, "Term" = description given by authors, § = infants older than one month post-term excluded, † = calculated from regression equation supplied by authors.

Table 1.2: Reference values for static respiratory system compliance (Crs) in ventilated neonates with respiratory distress syndrome. Data are range, mean (range), or mean ± SD unless stated otherwise.

First author	Method	No. of infants	Gestational age (weeks)	Weight (kg)	Length (cm)	Crs (ml/cmH_2O)	Crs ($ml/cmH_2O/kg$)	Crs ($ml/cmH_2O/m$)
Milner [188]	EIH	10	27 - 33	0.77 - 1.86	NG	0.37 (0.17- 1.82)	NG	NG
Milner [189]	EIH	6	25 - 33	0.78 - 2.02	NG	0.36 ± 0.22	0.27 ± 0.19	NG
Simbruner [60]	EIOT	9	28 -37	0.9 - 2.5	NG	0.46 ± 0.12	0.35*	NG
Lischka [62]	MOT	26	NG	1.5 ± 0.53	NG	0.61 ± 0.26	0.41*	NG
Dreizzen [14]	MOT	10	27 - 33	1.1 - 1.91	NG	0.76 ± 0.31	0.5 ± 0.19	NG
Pfenninger [115]	EIH	8	33 - 37	1.5 - 3.86	NG	0.7 ± 0.27	0.32 ± 0.08	NG
Morley [190]	EIH	46	23 - 29	1.034 ± 0.038 (SE)	NG	NG	0.53 ± 0.05 (SE)	NG
Pfenninger [191]	SBT	8	28 - 36	1.22 - 2.84	NG	NG	0.32 ± 0.08	NG
Baraldi [160]	SBT	20	30.5 ± 2.4	1.37 ± 0.45	NG	NG	O.4 ± 0.14	NG
Kelly [15]	SBT	22	24 - 33	0.560 - 2.03	NG	NG	0.41 ± 0.02	NG
Wilkie [63]	SBT	25	26 - 34	0.79 - 2.15	33 - 44	0.448 ± 0.171	0.359 ± 0.133	1.17 ± 0.41

EIH = end inspiratory hold, EIOT = end inspiratory occlusion technique, MOT = multiple occlusion technique, SBT = single breath technique, NG = data not supplied by authors, * = calculated from data supplied by dividing mean Crs by mean unit of body size.

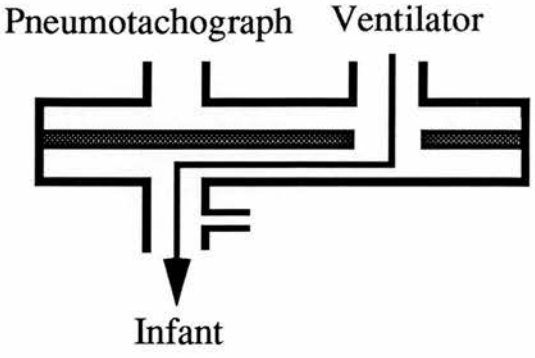
Apparatus

The apparatus used for all the lung mechanics measurements detailed in this thesis was constructed by the Medical Physics Department of Ninewells Hospital and Medical school, Dundee, under the guidance of Dr Rosalie Wilkie based on her experience working in Toronto with Dr A.C. Bryan. It is the same apparatus as that used in several previous studies in Canada and Scotland [59,63].

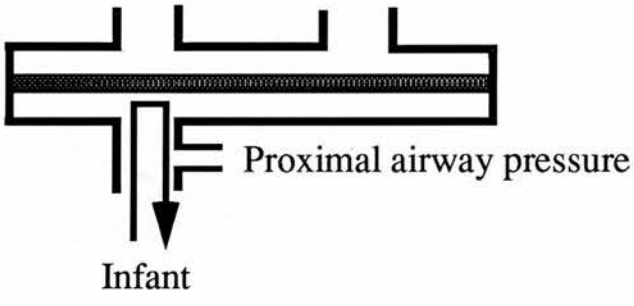
Breath sampling is done manually using a two-way airway occlusion device which is inserted into the ventilator circuit (fig. 1.1). This device is constructed of nylon and has wide bore channels to minimise resistance. The device can be thoroughly cleaned with alcohol between measurements. The dead space (measured by water displacement) added to the ventilator circuit by the occlusion device is 4mls. There is a rotatable slide-valve within the device which enables different channels to be opened or closed. The resistance of the occlusion device and pneumotachograph in series is essentially that of the pneumotachograph. With the device inserted into the ventilator circuit the infant is ventilated normally and the pneumotachograph is excluded from the circuit (fig. 1.1a). The device has a side port for sampling proximal airway pressure which is measured using a Furness Controls differential pressure transducer (0 - 10 kPa). Expiratory flow is measured with a Fleisch O pneumotachograph linear to 300 ml/s connected to a Validyne MP45 ($\pm$ 2cmH_2O) differential pressure transducer. Pressure and flow data are sampled at a frequency of 250 Hz and processed and stored on an on-line IBM compatible personal computer. Data is analysed using software developed at the Children's Hospital, Toronto by Professor A.C. Bryan, Dr M.H. Bryan and Dr P.N. LeSouef.

Figure 1.1: Airway occlusion device

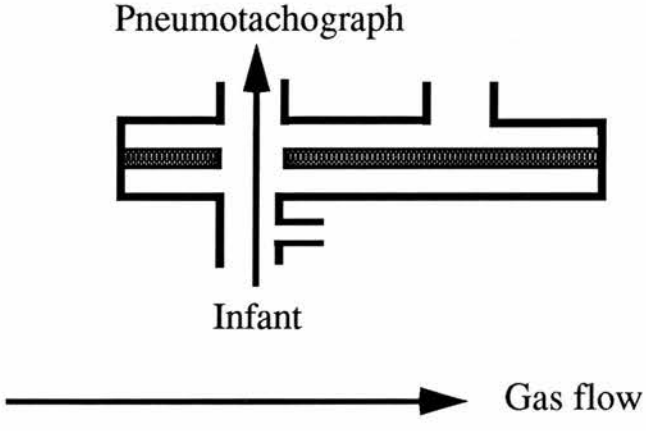
(a) Occlusion device inserted into ventilator circuit. Pneumotachograph is excluded from the circuit.



(b) Airway is occluded at peak inflation, trapping a breath in the infant's lungs. Proximal airway pressure is sampled.



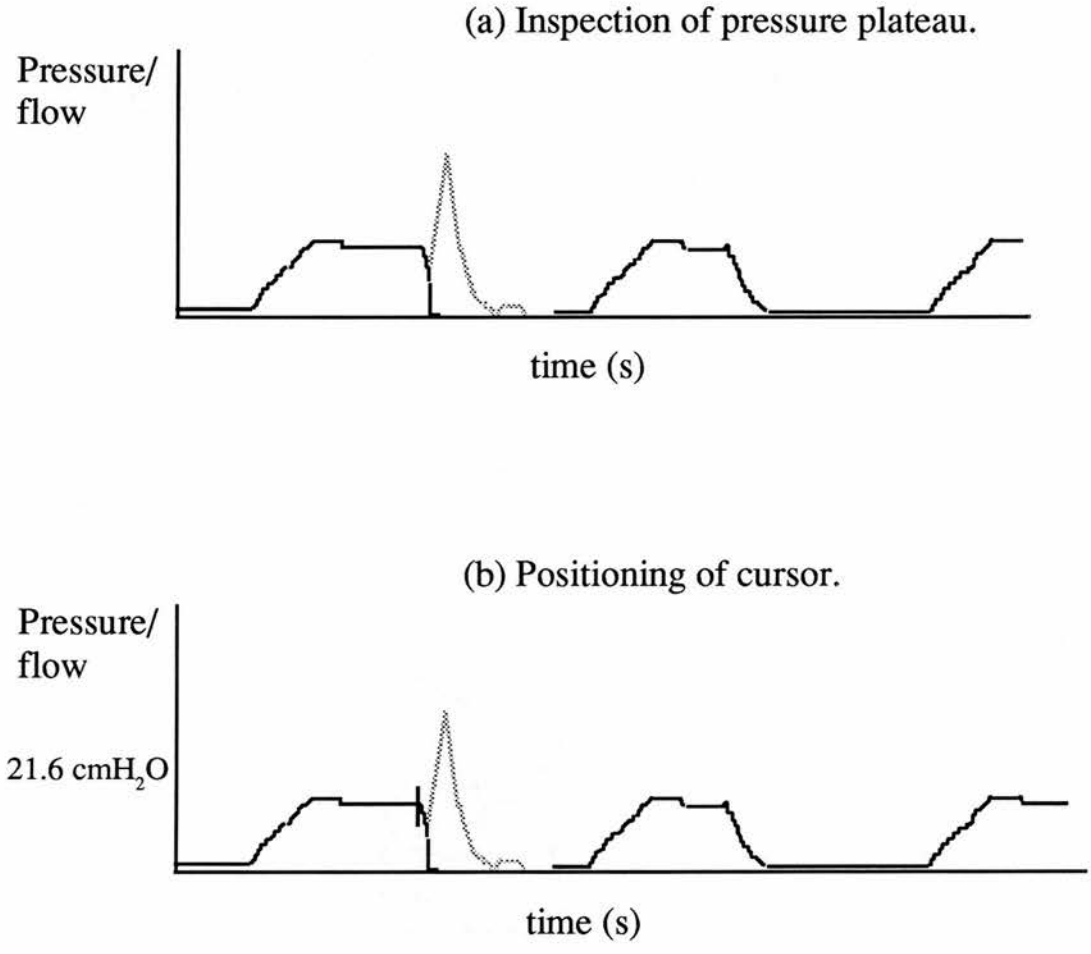
(c) Occlusion is released. Passive expiratory flow occurs through the pneumotachograph.



The program is called Rawfoot © and was written solely for this purpose. To sample a breath, the slide valve is manually rotated through 90° at the peak inflation pressure during a ventilator inflation. This occludes the infant's airway, trapping the ventilator breath in the lungs (fig. 1.1b) and usually induces a Hering-Breuer reflex. The occlusion is momentarily maintained to allow time for the proximal airway pressure to equilibrate with the alveolar pressure and during this time the proximal airway pressure is sampled continuously through a side port in the occlusion device. The slide valve is then rotated a further 90° this time excluding the ventilator from the circuit and allowing passive exhalation to occur to atmospheric pressure through the pneumotachograph (fig. 1.1c). The slide valve is then rotated back through 180° to its original position so that the procedure may be repeated. The whole breath sampling procedure takes no more than a few seconds and results in no significant disturbance to the infant. After the breath is sampled it can be viewed on screen to determine its suitability for analysis and during this time the infant is ventilated normally before the next breath is sampled. A number of satisfactory breaths are collected and their results averaged. The entire measurement procedure usually takes five to ten minutes.

During breath sampling the computer displays the data first in the form of a pressure-flow plot (fig. 1.2) and then as a flow-volume plot (fig. 1.3). The pressure-flow plot displays first the proximal airway pressure measured during sampling and then the passive expiratory flow, both against time. In fig. 1.2a the proximal airway pressure trace initially represents the positive end expiratory pressure set on the ventilator. There is then a sharp rise in pressure with a ventilator breath. The airway is occluded and there follows a pressure plateau. The occlusion is then released allowing proximal airway pressure to fall rapidly to zero and at this point the recording switches to passive expiratory flow as measured by the pneumotachograph. This starts at zero, rising rapidly to a peak and then falls back to zero.

Figure 1.2: Pressure-flow plot.



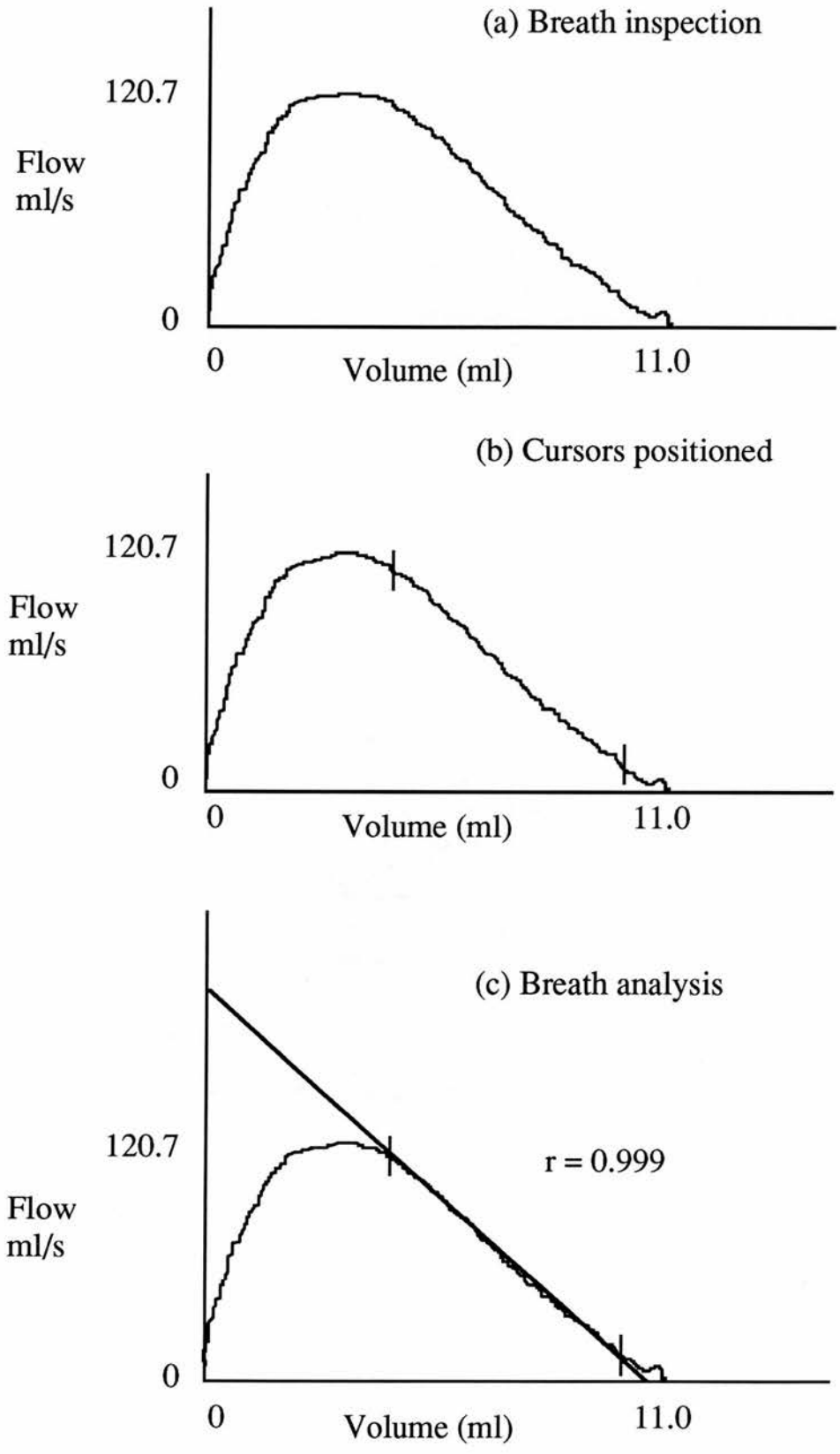
Proximal airway pressure during ventilation. Recording stops when ventilation is interrupted to sample passive expiratory flow.

Passive expiratory flow from peak inflation to atmospheric pressure.

Shortly afterwards the slide valve is rotated back to its starting position and the airway pressure trace resumes. The pressure plateau is inspected to determine that it is satisfactory. Its duration can be compared with that of the following ventilator breath. If the plateau is accepted and further breath analysis is desired, the airway pressure just prior to release of the occlusion is selected by positioning a cursor (fig. 1.2b). This is the pressure that will be used to calculate the compliance when the flow-volume trace is analysed. Once the cursor is positioned and entered the computer displays the flow-volume trace (fig. 1.3a) for inspection. The actual expired volume and maximal expiratory flow are given. If the breath appears satisfactory in terms of linearity, morphology and expired volume, the linear portion can then be selected for analysis by positioning two cursors (fig. 1.3b). The computer analyses all the data points between these two cursor points using linear regression and plots a straight line of best fit (fig. 1.3c). The line is extrapolated to the volume axis to give the expired volume at zero flow and this is divided by the occlusion pressure determined earlier to give the respiratory system compliance. The slope of this line is the time constant and dividing this by the compliance gives the respiratory system resistance.

The software includes a calibration run which enables the pneumotachograph to be calibrated to known flows and pressures and the accuracy of volume estimations can be checked with a syringe. Calibration was performed weekly throughout the studies, previous experience with this apparatus indicating that drift over this length of time was minimal. The pneumotachograph was calibrated using air. The ideal would be to calibrate the apparatus before each study with the same gas mixture as that being breathed by the infant, as different gas mixtures have different viscosities and will cause slightly different pressure drops across a pneumotachograph at identical flow rates. The very large number of studies to be done made this impracticable.

Fig 1.3: Flow - volume plots



Oxygen is more viscous than air so at the same flow rates 100% oxygen would cause a pressure drop across a pneumotachograph approximately 9-10% greater than that caused by air [192,193]. This would cause a 9% overestimation of expiratory flow and therefore compliance in infants breathing 100% oxygen compared to those breathing air. As the respiratory function of these infants improved and their inspired oxygen concentration was reduced, their improvements in compliance would be slightly underestimated as a result. The pressure transducer was calibrated using a water manometer.

To maximise comparability we applied the same data acceptance criteria in all the studies described later in this thesis.

1. Only ventilator generated breaths were analysed (only intubated infants were studied).

2. All infants were studied lying supine whilst breathing quietly and not displaying gross body movement.

3. Studies were performed soon after endotracheal suction.

4. Results calculated from a minimum of three, preferably four or more technically satisfactory breaths with a coefficient of variation between breaths $\leq 15\%$.

5. Clearly defined pressure plateau following airway occlusion lasting approximately 200ms.

6. Actual expired volume to atmospheric pressure 5 - 10ml/kg body weight.

7. Linear portion of the flow/volume trace approximately 2/3 or more of the expiration from peak expiratory flow to zero flow.

8. Correlation coefficient of the straight line fit to the linear portion of the flow-volume trace $r > 0.996$.

In practice it is relatively easy to fulfil these criteria in the majority of cases. They were applied as absolute criteria except for the actual expired volume which was occasionally above or below 5-10 ml/kg. These studies were accepted as half of the compliance data collected was blind to the clinicians caring for these infants and ventilator adjustment would have been required to alter the expired volume range.

Summary

This thesis represents an evaluation of the potential of routine measurements of static respiratory system compliance made using the single breath passive-expiratory flow technique to improve the care of ventilated newborn infants. The measurement technique has been validated in newborn infants and used in many studies. Because it is dependent on the respiratory system behaving as a single homogeneous compartment and the measurement conditions being carefully controlled there may be circumstances where reliable data is unobtainable. Although there are a number of techniques available for measuring respiratory function in ventilated infants, no technique is without problems and no technique has been demonstrated in a randomised study to improve the outcome of neonatal ventilation.

Chapter 2: Reliability of Clinical Assessments of Static Respiratory System Compliance

Introduction

Whenever an infant is mechanically ventilated an informal clinical appraisal of the respiratory system compliance is made by the individual deciding on the ventilator settings. They estimate the chest inflation and therefore the tidal volume that is being delivered by the ventilator settings in use. Other clinical observations such as the chest radiographic findings and the oxygen requirements may influence their decision and there is often blood gas data outlining the infant's response to the current ventilator settings. All this information is combined with the knowledge and experience of the care-giver and the most appropriate ventilator settings are decided on. But the accuracy of clinical judgements is likely to vary with the experience of the observer making them. Aufricht et al [57,194] suggested that senior experienced clinicians can make reliable visual judgements of static respiratory system compliance based on assessment of tidal volume in two papers examining the abilities of doctors to estimate compliance. This is the only published work on the topic in infants. Closer scrutiny of their data [57] suggests that they may not have been as accurate as they believed themselves to be. The mean (sd) difference between the estimated and measured compliance was given as -7 (24)% and it was concluded that the estimates agreed with the measurements to within 24%. The compliance values were not corrected for patient size.

This may have contributed to the relatively high correlation coefficient of r=0.81 as the range of values was wider than it would have been after correction for size, and the wider the numerical range of any two variables that are compared the better the correlation coefficient will be [195]. The authors felt that an error of ± 24% was acceptable given the wide range of compliance values from severe abnormality to complete normality, but since they used the mean difference ± one standard deviation to calculate this potential error, fifteen out of their forty-five observations lay outside these limits (as would be expected). This demonstrates the inadequacy of using one standard deviation as a measure of agreement between methods.

Bland and Altman [195] suggested that a more reliable way of comparing different methods of measurement would be to express the 95% limits of agreement. These are the limits within which 95% of differences between two methods of measuring the same parameter would be expected to lie and are expressed by the mean difference ± 2 standard deviations. For Aufrichts' study [57] they would be -55 to + 41%. Examined in this way the agreement between the estimates and measurements does not appear as close and since it is often junior doctors that are managing the ventilation of infants this observation may be important. It was suggested in the paper, but data was not supplied, that junior doctor's estimates were not as accurate. Spears showed that even senior anaesthetists manually ventilating infant test lungs using the anaesthetic circuits that they commonly used on infants of similar size were unable to detect when the endotracheal tube was repeatedly occluded [58]. Chest radiographs may give valuable clinical information but it can be difficult to determine the diagnosis from them alone particularly in neonates [55,56] and, as a measure of disease severity, assessment of chest radiographs performed less well than compliance results at predicting death from respiratory distress syndrome [62]. Blood gas analysis is an essential clinical tool in managing ventilated patients but it is a measure of the effect of the current ventilator settings rather than a measure of what they ideally might be.

As discussed already, it is possible to cause the blood gas tensions significantly to worsen, particularly the oxygenation, by over- or under-ventilation. The clinicians who conduct most of the care of ventilated infants are usually in training and will almost always have access to expert help but may not refer to it. Despite considerable improvements in the outcomes of ventilated newborn infants there continue to be a significant number of infants who die of respiratory failure during the acute stages of their lung disease or who develop other serious problems such as pneumothorax or bronchopulmonary dysplasia. Any objective information about lung function that might help tailor the ventilation strategy to the individual's needs might be expected to prove beneficial given the subjective nature of the other information available. On the other hand if junior doctors can reliably judge respiratory mechanics then the additional handling associated with making the measurement however minimal would be hard to justify outside the research setting. This study was designed to determine whether the different grades of junior doctors involved in the ventilator care of infants in a regional intensive care unit were able reliably to judge respiratory system compliance clinically.

Patients and methods

This study was made on 46 newborn infants mechanically ventilated from the early hours of life and enrolled in a randomised controlled trial of compliance measurements. Infants were eligible for inclusion in the study if the Senior House Officer, Registrar and Research Fellow involved in the care of the infant were available to make estimates of compliance at the same time and no preceding compliance measurements had been made.

Compliance Estimates

As soon as possible after ventilation was commenced the three observers made estimates of the static respiratory system compliance using 2 methods: (a) optical compliance (Crs_{op}), and (b) analogue compliance (Crs_{an}). Optical compliance is derived from assessment of tidal volume [57,189]. The tidal volume delivered by the ventilator is estimated from the degree of chest inflation visible. The observer decides whether the chest inflation is less than normal and barely visible, approximately normal, or greater than normal and distinctly visible (normal being that which would be observed in a healthy newborn infant breathing spontaneously). A tidal volume of 5, 7.5 or 10 mls per kg body weight is assigned accordingly. These values are then multiplied by the body weight of the infant to give the total estimated tidal volume which is then divided by the pressures set on the ventilator (peak inspiratory pressure minus positive end-expiratory pressure) to give the optical compliance. One limitation of this method is that it only allows for 3 possible values of optical compliance for each set of ventilator settings which could limit its accuracy. In view of this we assessed the potential of estimates made using a linear analogue scale to perform more reliably. Junior doctors were asked to mark a cross on a linear analogue scale corresponding to what they thought the Crs would be. They were given a line 21cm long which on a linear scale described possible Crs values corrected to body length ranging from 0.4 to 2.5 ml/cmH_2O/m (fig 2.1) They were told that this described the range of values from worst possible to normal. There were two pre-existing marks on the scale at 0.6 ml/cmH_2O/m and 1.8 ml/cmH_2O/m to assist them in their estimates. The observers were told that a Crs of 0.6 ml/cmH_2O/m corresponded to very stiff lungs and a high incidence of morbidity and mortality as demonstrated in a previous study using the same apparatus [59] and that the lowest Crs value recorded from more than 100 ventilated newborn infants during the previous year was 0.5ml/cmH_2O/m.

The junior staff were told that a Crs of ≥1.8 ml/cmH_2O/m was indicative of minimally stiff lungs as infants with compliance values greater than or equal to this had been found to have normal lung phospholipid profiles in another study with the same apparatus [63] and in our experience these infants had not responded well to surfactant replacement therapy [196]. The observers were told that the compliance of 2.5 ml/cmH_2O/m at the upper extreme of the scale corresponded to normality. There are no substantial reference data for the normal values of compliance using this method in ventilated infants since normal infants are not usually ventilated. In our experience up to the beginning of this study infants recovering from lung disease were usually well enough to be extubated and were often breathing air by the time their compliance had reached 2.5 ml/cmH_2O/m. The median (quartile) static respiratory system compliance measured within the 24 hours before extubation of 144 infants successfully extubated (not re-intubated within 24 hours) during the randomised trial described in this thesis was 2.6 (2-3.2) ml/cmH2O/m. Normal non-intubated infants have static compliance values of around 5-7.8 ml/cmH_2O/m or 1.1-1.5 ml/cmH_2O/kg [83,114,126,178,187] and in our experience infants ventilated for reasons other than lung disease can have compliance values of 5 ml/cmH_2O/m or more. "Normal" in the context of this study therefore represented functional normality as defined by a respiratory system compliance value not usually associated with the need for mechanical ventilation for a pulmonary cause. For the purposes of comparison all measured and optical compliance values that were greater than 2.5ml/cmH_2O/m were called 2.5. The estimates using both methods were made simultaneously and each observer was blind to the estimates of the other observers. The senior house officer and registrar were often in possession of other data at the time of their estimates such as blood gas data or x-ray findings and at least one of them would have hand-ventilated the infant in the labour ward resuscitation room prior to transferring the infant to the neonatal unit.

Fig. 2.1: Data sheet for documenting estimates of analogue and optical Crs

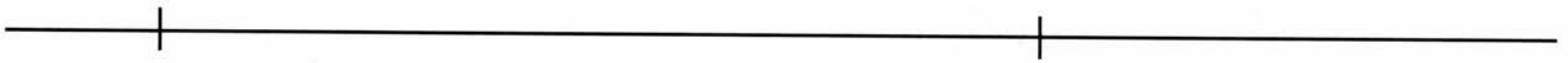
NAME. _____

STUDY NO. _____

DATE. _____

GRADE OF DOCTOR. _____

ANALOGUE COMPLIANCE.



0.6 Or less
(very stiff lungs)

1.8 Or more
(minimal or no lung stiffness)

ESTIMATED TIDAL VOLUME (ml/kg) 5 7.5 10

Compliance measurements

Immediately following the estimates the Crs was measured by the research fellow who was blind to the estimates made by the senior house officer and registrar at the time of measurement. The measurements were made using the single breath passive expiratory flow technique, applying the same data quality control standards and using the same apparatus described in chapter 1.

Statistical methods

The 95% limits of agreement between the estimates and the measurements were calculated for each grade of junior doctor and for each method of Crs estimation. These were expressed as percentages of the measured Crs. To give a comparison between this and the previous studies, the agreement was also assessed by the correlation coefficients calculated by linear regression. The agreement between the two methods of estimation was also determined using the same methods.

Results

From the start of this study until the randomised trial finished, 72 infants were available for enrolment. Satisfactory data was collected from 46 infants (64%). On 8 (11%) occasions the junior doctors were not available and on 18 (25%) occasions the compliance measurement was not successful. The baseline characteristics of the 46 studied infants are described in table 2.1 and the results comparing the estimations and measurements of Crs are outlined in tables 2.2-2.8. Figures 2.2 and 2.3 show the differences between each measurement and the corresponding estimates plotted against the measurements. The estimates of all 3 observers are combined in each plot as the patterns were similar between observers.

Table 2.1: Patient characteristics. Data are median (range)

n	46	
Gestational age (weeks)	31	(25-41)
Birthweight (kg)	1.496	(0.553 - 4.050)
Length (cm)	40	(29 - 57)
Crs (ml/cmH_2O)	0.519	(0.174 - 3.744)
Crs ($ml/cmH_2O/m$)	1.3	(0.5-7.8)
Crs ($ml/cmH_2O/kg$)	0.368	(0.175 - 1.138)

Table 2.2: Agreement between optical or analogue estimates and measured Crs (corrected to length). Limits of agreement are % of the measured Crs.

	Correlation coefficient		**95% limits of agreement**	
Observer	**Crs_{op}**	**Crs_{an}**	**Crs_{op}**	**Crs_{an}**
SHO	r=0.616	r=0.631	-87%, +63%	-72%, +69%
Registrar	r=0.631	r=0.434	-86%, +61%	-121%, +89%
Research Fellow	r=0.673	r=0.680	-93%, +63%	-94%, +67%

Table 2.3: Agreement between optical or analogue estimates and measured Crs (corrected to weight). Limits of agreement are % of the measured Crs.

	Correlation coefficient		**95% limits of agreement**	
Observer	**Crs_{op}**	**Crs_{an}**	**Crs_{op}**	**Crs_{an}**
SHO	r=0.339	r=0.646	-87%, +63%	-72%, +69%
Registrar	r=0.421	r=0.404	-86%, +61%	-121%, +89%
Research Fellow	r=0.525	r=0.623	-93%, +63%	-94%, +67%

Table 2.4: Agreement between optical or analogue estimates and measured Crs (not corrected for body size). Limits of agreement are % of the measured Crs.

	Correlation coefficient		**95% limits of agreement**	
Observer	**Crs_{op}**	**Crs_{an}**	**Crs_{op}**	**Crs_{an}**
SHO	r=0.787	r=0.785	-87%, +63%	-72%, +69%
Registrar	r=0.796	r=0.710	-86%, +61%	-121%, +89%
Research Fellow	r=0.827	r=0.835	-93%, +63%	-94%, +67%

Table 2.5: Agreement between optical estimates and measured Crs (corrected to body length). All estimated and measured values > than 2.5ml/cmH_2O/m included as their actual values rather than limited to 2.5 ml/cmH_2O/m. Limits of agreement are % of the measured compliance.

	Correlation coefficient	**95% limits of agreement**
Observer	**Crs_{op}**	**Crs_{op}**
SHO	r=0.632	-90%, +74%
Registrar	r=0.721	-90%, +70%
Research Fellow	r=0.705	-97%, +72%

Table 2.6: Agreement between estimates of optical and analogue compliance for each grade of observer (corrected to length). Limits of agreement are percentages of the optical compliance.

Observer	**Correlation coefficient**	**95% limits of agreement**
SHO	r=0.463	-80%, +70%
Registrar	r=0.404	-87%, +72%
Research Fellow	r=0.483	-76%, +80%

Table 2.7: Distribution of tidal volume estimates by grade of observer.

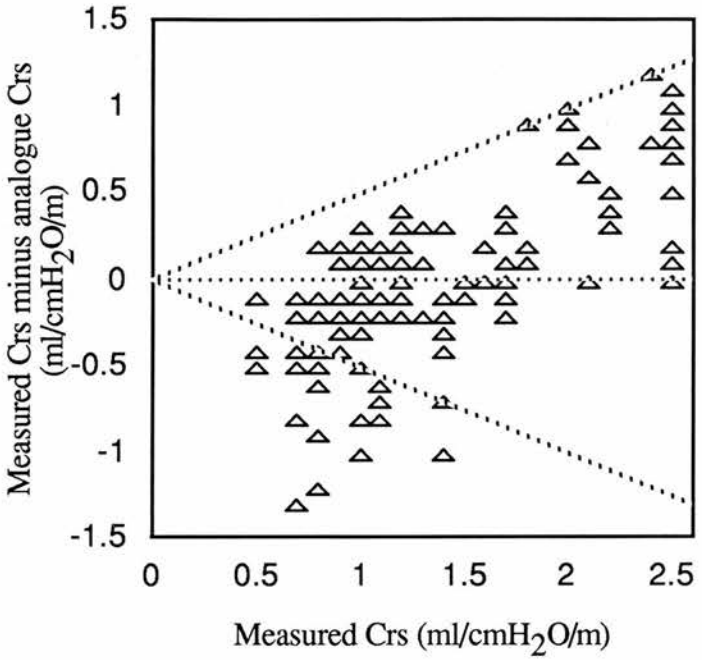
	Estimated tidal volume		
Observer	**5ml/kg**	**7.5ml/kg**	**10ml/kg**
SHO	2	35	9
Registrar	2	36	8
Research Fellow	6	34	6

Table 2.8: Population distribution of values for measured static respiratory system compliance and analogue estimates by grade of observer.

Variable	**Coefficient of variation**
Measured Crs	42%
SHO Analogue estimate	30%
Registrar analogue estimate	27.1%
Research Fellow analogue estimate	28.9%

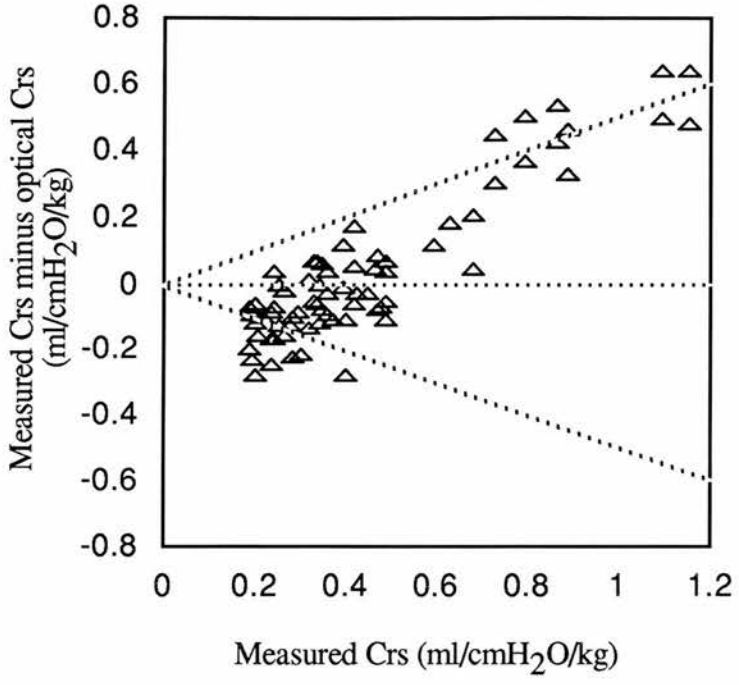
For all three grades of observer the agreement between estimates and measurements of Crs corrected to body length was poor whether assessed by the correlation coefficient or by the 95% limits of agreement (table 2.2). There was little difference between the grades of observer. As would be expected there was no difference in the 95% limits of agreement whether the results were expressed uncorrected for body size, or corrected to length or weight (tables 2.2, 2.3 and 2.4). The mode of correction for size did however have a dramatic effect on the correlation coefficients (tables 2.2, 2.3 and 2.4). The correlation coefficient (r) for the relationship between the optical compliance estimates and the measured compliance for the Senior House Officers was 0.339 when the values were corrected to body weight, 0.616 when corrected to length and 0.787 when uncorrected for body size. Of the 46 infants, 5 (11%) had measured Crs > 2.5 ml/cmH_2O/m. The values were 2.8, 3.3, 3.5, 5.4, and 7.8. The data for all 46 infants were re-analysed with those infants whose measured or optical compliance was greater than 2.5 ml/cmH_2O/m analysed according to their actual values rather than assigned a value of 2.5 ml/cmH_2O/m (table 2.5). In all cases the 95% limits of agreement got slightly wider, indicating worse agreement, whereas by contrast the correlation coefficients improved (tables 2.2 and 2.5). When the optical and analogue estimates were compared to one another rather than to the measured compliance they too showed poor agreement both in terms of the correlation coefficients and the limits of agreement (table 2.6). Despite this, neither method of estimating the measured compliance was superior. They agreed poorly both with each other and with the measured compliance. When estimating the optical compliance (table 2.7), all three grades of junior doctor usually selected the middle tidal volume option of 7.5 mls/kg (105/138=76% of occasions). A similar observation could be made about the analogue compliance estimates as these were more closely distributed around their mean than the measured compliance values (table 2.8).

Figure 2.2: Difference between measured and analogue Crs plotted against measured Crs.



Diagonal dotted lines represent ± 50% of the measured Crs.

Figure 2.3: Difference between measured and optical Crs plotted against measured Crs.



Diagonal dotted lines represent ± 50% of the measured Crs.

Figures 2.2 and 2.3 demonstrate that for both methods of estimation this meant that the observers tended to overestimate the Crs of the infants with the lowest Crs and to underestimate the Crs of the infants with higher Crs. The observers differed by more than one category of estimated tidal volume on two occasions. The differences between the estimates and the measurements was calculated by subtracting the estimated value from the measured value in all cases. The estimates using both methods were on average slightly higher than the measurement for all three grades of observer as demonstrated by the negative weighting of the limits of agreement (tables 2.2, 2.3 , 2.4).

Discussion

This study clearly demonstrates that junior doctors' estimates of Crs are unreliable. Neither method of estimating Crs performed within acceptable limits of accuracy to represent a realistic alternative to direct measurement. The limitations of using linear regression to assess the agreement between two methods of measuring the same parameter are demonstrated by the large variations in the correlation coefficient. It might have been concluded if only uncorrected estimates were considered that the estimates showed acceptable agreement with the measurements as the correlation coefficients ranged from r=0.710 to r=0.835 but the limits of agreement were all wide. As has been discussed, correction of Crs measurements for size is important if they are to represent disease severity. Narrowing the range over which Crs measurements were considered in order to accommodate the analogue scale led to a slight overestimation of the accuracy of the optical estimates but despite this they still performed poorly.

It is possible that this also led to a marked overestimation of the accuracy of the analogue estimates and that they would have been much worse than the optical estimates if considered over a wider range but since they too were unreliable in the narrower range this is immaterial. It is interesting and disappointing that the two methods of estimating Crs agreed so poorly with one another when they were developed to assess the same parameter.

The junior doctors mostly chose the intermediate tidal volume when estimating the optical Crs. This was also the finding of Aufricht et al [57]. They attributed the poorer performance of the junior doctors when compared to a senior neonatologist partly to this apparent preference for selecting the middle value. It is a weakness of the method of assessing optical Crs that it starts with an assumption that the ventilator settings are appropriate by limiting the tidal volume options to a range of 5-10mls/kg. Normal non-ventilated infants have mean tidal volumes ranging from 7-9 ml/kg [139] so 5-10ml/kg is probably within an acceptable "normal" range for ventilated infants and does not really describe chest inflation that is either less than normal and barely visible, or greater than normal and distinctly visible. As such optical Crs estimation cannot be expected to detect inappropriate ventilator settings which might be one important clinical role for Crs measurement [59]. The observers differed by more than one tidal volume category on 2 out of 46 occasions. Considering that this required one observer to think that the tidal volume was less than desirable and barely visible whilst another simultaneously thought that it was greater than desirable and distinctly visible it should give us pause. Both the optical and analogue estimates were made during tidal ventilation. It could therefore be argued that they are more a reflection of dynamic than static respiratory system compliance. If this were so they might be expected to be lower on average than the static respiratory system compliance values yet they proved to be higher.

The measured Crs may not be the appropriate gold standard. The more important question is what gives the best indicator of disease severity and is therefore most relevant and potentially useful in clinical practice. There is already much evidence that Crs measurements may provide clinically useful information. In 1982 Crs measurements were found reliably to measure respiratory disease severity and predict clinical outcome [60]. Ten years on these findings have been confirmed [59] although the Crs values associated with a high risk of death are now appreciably lower presumably as a result of improvements in care. Tarnow-Mordi et al [59] also showed that Crs measurements may be a more reliable measure of disease severity than oxygen requirements in ventilated infants. Crs can predict biochemical lung maturity [63] and may also measure the response to surfactant [15] and later the risk of developing bronchopulmonary dysplasia [197]. They have been used to measure the response to bronchodilators [198,199,200]. They may also identify infants suitable for extubation [64]. None of these studies demonstrate that the use of Crs measurements in routine clinical care can improve outcome in an important way. This will be necessary if lung function testing is to become widely popular. It should be remembered that in this study 25% of Crs measurements were unsuccessful which may limit their usefulness.

Chapter 3: Randomised Controlled Trial of Respiratory System Compliance Measurements

Introduction

There seems little doubt from the breadth of the available data that making routine measurements of respiratory mechanics as an adjunct to clinical management would be a feasible aim. Studies identify many specific areas of clinical management where additional information about respiratory function might prove useful. Nevertheless the commercially available technology required to make respiratory function measurements is expensive. The measurements themselves have limitations and their rigorous interpretation requires expert knowledge. There are many circumstances where the data obtained may be uninterpretable or misleading. More information is required about the reliability of the techniques. The introduction of many new modalities of ventilation has made the process of ventilation extremely complicated for the junior doctors that care for preterm infants and further information overload may be counterproductive. The question remains therefore whether in a more global sense the adoption of respiratory function testing into practice will result in some measurable improvement in clinical outcomes or resource utilisation. There are no published studies that address this question directly. We therefore performed a randomised controlled trial of conventional clinical management (control group) versus clinical management supplemented by routine information on Crs (experimental group) in two Scottish neonatal units

We wished to determine whether the experimental group would have

(a) fewer adverse clinical events. Defined for this study as death before discharge, or receiving mechanical ventilation at 15 days, or breathing supplementary oxygen at 36 weeks post conception, or pneumothorax, or pulmonary interstitial emphysema (PIE), or pulmonary haemorrhage, or abnormal cerebral ultrasound scan (USS) appearances at 6 weeks postnatal age.

(b) improved lung function, assessed by greater mean Crs after the first 48 hours of life.

(c) fewer days of respiratory support by endotracheal tube.

(d) fewer days in 40% oxygen.

(e) fewer days in supplementary oxygen.

(f) fewer doses of surfactant.

Patients and methods

All neonates receiving mechanical ventilation by endotracheal tube in the neonatal intensive care units of the Simpson Memorial Maternity Pavilion in Edinburgh and Ninewells Hospital and Medical School in Dundee between August 1991 and June 1993 were considered for inclusion in the study. Infants were not enrolled if it was felt by the responsible clinician that their inevitable death was imminent or if a life threatening congenital abnormality was apparent in the immediate neonatal period. Written parental consent was obtained in all cases.

Infants were randomised by the opening of a sealed, numbered envelope. Randomisation was stratified by treatment centre. All aspects of the clinical management of the control group was conducted according to the normal practice in each centre. In addition, Crs was measured by the clinical research fellow in each infant, using the single breath technique as soon as possible after endotracheal intubation, at least daily for the first seven days of ventilation and twice weekly thereafter until extubation. Additional measurements were made immediately before and 3 and 12 hours after each dose of surfactant. The results of these Crs measurements were not made available to clinical staff. The experimental group were managed in the same way as the control group except that the results of each Crs measurement were routinely entered on the blood gas recording sheet where they would be frequently seen by the clinical staff adjusting the ventilator. The measurements were corrected to body length to give units of ml/cmH_2O/m. Guidelines to assist the clinical staff in the interpretation of Crs were entered on the clinical record alongside the Crs data (table 3.1). They were based on two previous studies using the same apparatus in the nurseries of Ninewells Hospital in Dundee and Mount Sinai Hospital in Toronto, Canada [59,63].

Table 3.1: Clinical guidelines based on Crs data.

Crs < 0.6 ml/cmH_2O/m indicates very stiff lungs.	Not advisable to reduce ventilator support.
Crs 0.6 - 1.2 ml/cmH_2O/m indicates moderately stiff lungs.	Weaning may be justified if clinically improving.
Crs 1.2 - 1.8 ml/cmH_2O/m indicates mild to moderate lung stiffness.	Try weaning. Aim for I:E < 1:2, PIP < 21, PEEP < 4.
Crs >1.8 ml/cmH_2O/m indicates minimal or no lung stiffness.	Try weaning. Aim for I:E < 1:2, PIP < 21, PEEP < 4.

Because they were "unblinded" as to Crs data, the research fellows were not part of the clinical team managing the infants. They were available to explain the Crs data but did not make management decisions. It was calculated that a sample size of 104 infants in each group would yield >80% power to show a reduction from 40% to 20% in the combined rate of adverse clinical events at the 5% level of significance using a 2 tailed test. This sample would also provide >80% power to demonstrate a reduction in median duration of respiratory support by endotracheal tube from 7 to 4 days. Differences in proportions of categorical data were compared using the χ^2 test. Differences in continuous data were compared using the Mann-Whitney U test.

Results

Two hundred and forty-five eligible infants were enrolled into the study. Their characteristics at study entry are shown in table 3.2. The two groups did not differ significantly in birthweight, gestational age, length, initial Crs, frequency of antenatal steroid exposure or Apgar scores. The experimental group contained by chance a significantly greater proportion of males than the control group.

Problems with data collection

Because of difficulties resulting from air leaks around the endotracheal tube, non-linear expired flow-volume plots and failure to induce relaxation the Crs measurements were often unsuccessful. The initial measurement at study entry was successful in 102 of 123 infants (83%) in the experimental group and 94 of 122 controls (77%) giving an overall success rate of 80%. In 25 (10%) infants, no successful measurements at all were made (11 infants in the experimental group and 14 in the control group). The infants with no successful Crs data tended to have been ventilated for less time than those with successful data collection. The median (range) duration of ventilation of the infants with no successful measurements was 2 (1-13) days compared to 5 (1-114) days for the study population as a whole.

Table 3.2: Population characteristics at study entry. Data are median (range) or number (%).

	Control Group	Experimental Group	
n	122	123	
Birth weight (g)	1423 (580 - 5250)	1426 (452 - 4400)	p = 0.69
Birth length (cm)	40 (30 - 57)	40 (29 - 55)	p = 0.65
Gestation (weeks)	31 (23 - 42)	30 (25 - 42)	p = 0.94
Gender (M/F)	62/60 (51%:49%)	79/44 (64%:36%)	p = 0.046
Antenatal steroids	37 (30%)	44 (36%)	p = 0.44
Initial Crs	1.5 (0.5 - 7.9)	1.4 (0.5 - 5.6)	p = 0.34
Inborn	106 (87%)	110 (89%)	p = 0.675
Delivery mode			
Vaginal	63 (52%)	56 (46%)	
C/S in labour	22 (18%)	26 (21%)	
C/S no labour	37 (30%)	41 (33%)	p = 0.623
Singleton	99 (81%)	99 (80%)	p = 0.975
Apgar at 1 minute	5 (0 - 9)	5 (0 - 9)	p = 0.25
Apgar at 5 minutes	8 (0 - 9)	8 (1 - 9)	p = 0.59

Primary outcomes

Adverse clinical events: The numbers of infants in each group with each adverse clinical event are given in table 3.3. There were no significant differences between the two groups for any individual adverse event or in the total number of infants in each group with any averse event.

Table 3.3: Frequencies of adverse events. Data are number (%)

	Control Group	Experimental group	
n	122	123	
Death	16 (13%)	19 (15%)	p = 0.735
Ventilator dependent day 15	27 (22%)	24 (20%)	p = 0.728
O_2 dependent at 36 weeks	24 (20%)	23 (19%)	p = 0.975
Pneumothorax	11 (9%)	9 (7%)	p = 0.800
PIE	12 (10%)	10 (8%)	p = 0.808
Pulmonary haemorrhage	10 (8%)	7 (6%)	p = 0.603
Abnormal USS at 6 weeks	14 (11%)	18 (15%)	p = 0.586
Any adverse event	54 (44%)	54 (44%)	p = 0.943

Lung function at 48 hrs: Forty-two infants were extubated on the first day after study entry (21infants in each group). A further 39 infants were extubated on their second day in the study (24 infants in the experimental group and 15 controls). Crs results were obtained on day two in 108 infants (62 infants in the experimental group and 46 controls). There was no significant difference in the distribution of the Crs values of the two groups. The experimental group had a median (quartile) Crs of 1.3 (0.8-2.2) ml/cmH_2O/m. The corresponding values for the controls were 1.3 (0.9-1.9) ml/cmH_2O/m (p = 0.92).

Duration of ventilation: Infants in the experimental group required respiratory support by endotracheal tube for a median (quartile) 4 (2-9) days compared to 5 (2-12) days for the controls (p = 0.20). Excluding the 19 infants in the experimental group and the 16 control infants that were still intubated at the time of their deaths, the median (quartile) ages in days at final extubation were 4 (2-10) for the experimental group and 5 (2-21) for the controls (p = 0.048).

Oxygen supplementation: Data on oxygen supplementation are presented in table 3.4. There were no significant differences between the two groups in duration of requirement for greater than 40% oxygen or in duration of requirement for any supplemental oxygen.

Table 3.4: Duration of oxygen supplementation. Data are median (quartile).

	Control group	Experimental group	
n	122	123	
Days in > 40% oxygen	2 (1-8)	3 (1-5)	p = 0.87
Days in oxygen	6 (2-34)	6 (3-36)	p = 0.71

Surfactant treatment: During the study period infants were considered eligible for surfactant treatment if they were less than 72 hours old, had no major congenital malformation, had a clinical and radiological diagnosis of respiratory distress syndrome and an arterial/alveolar oxygen tension (a/A) ratio < 0.22 . The same criteria and the same surfactants were used in both centres. The decision whether or not to give surfactant was not based on the Crs data. At the time that this study began on 5/8/91 both centres were already participants in the Curosurf IV multicentre study [201]. Curosurf IV finished at the beginning of 1992 and the last Curosurf was given on 15-1-92 in Edinburgh and on 26-2-92 in Dundee. The Curosurf IV study was a comparison of 2 different dose regimens for Curosurf. Infants were randomised to receive either a high dose regimen (initial dose 200mg/kg followed by up to four further doses of 100mg/kg at 12 hour intervals thereafter if clinically indicated) or a low dose regimen (initial dose 100mg/kg with up to two further doses of 100mg/kg at 12 hourly intervals thereafter if clinically indicated). From the end of the Curosurf IV study onwards, infants in both centres received Exosurf 5ml/kg according to the above criteria, with up to two repeat doses at 12 hour intervals if clinically indicated.

Following the publication of the OSIRIS study [202] in 1992 the number of repeat doses of Exosurf permitted was reduced to one. The details of surfactant administration to the two groups are detailed in table 3.5. There were no significant differences in the number of infants in each group that received surfactant, the surfactant regimens used or the total number of surfactant doses administered to each group.

Table 3.5: Surfactant administration. Data are number (%).

	Control Group	Experimental Group	
n	122	123	
Received surfactant	62 (51%)	60 (49%)	p = 0.848
High dose Curosurf	9	8	
Low dose Curosurf	17	15	
Exosurf	36	37	p = 0.920
Total doses	121	115	

Other outcomes

Remaining outcome data are detailed in table 3.6. There were no significant differences between the two groups in the frequencies of development of chronic lung disease (CLD), defined as requiring supplemental oxygen and having an abnormal chest x-ray at 28 days of age, or persistent ductus arteriosus (PDA) requiring clinical intervention. Similar numbers of infants in the two groups were treated with steroids and intralipid. There were no differences in the patterns of cranial ultrasound abnormalities during the first week of life. The median duration of hospitalisation was identical for the two groups.

Table 3.6 study outcomes. Data are median (quartile) or number (%).

	Control Group	Experimental Group	
n	122	123	
CLD	31	26	p = 0.522
Steroids for CLD	23	20	p = 0.715
Significant PDA	29	19	p = 0.139
Given intralipid	47	48	p = 0.96
Abnormal USS week 1	35	34	p = 0.968
Subependymal bleed	9	11	p = 0.830
Intraventricular bleed	15	13	p = 0.823
Periventricular bleed	10	5	p = 0.279
Days in hospital	40 (21 - 67)	40 (21-65)	p = 0.97
Sum days in hospital	6311	6167	
Sum days intubated	1429	1186	

Secondary analysis - survivors only

Secondary analysis was performed according to whether or not infants survived to determine the quality of outcomes in the survivors and to examine the possibility that the primary analysis was skewed by the survival in the experimental group of infants who might otherwise have died. Nineteen infants in the experimental group and 16 in the control group died. The characteristics of the surviving infants are shown in table 3.7. Again the two groups did not differ significantly in birthweight, gestational age, length, initial Crs, frequency of antenatal steroid exposure or Apgar scores. The experimental group still contained a significantly greater proportion of males than the control group.

Table 3.7: Characteristics of survivors. Data are median (range) or number (%).

	Control group	**Experimental group**	
n	106	104	
Birth weight (g)	1525 (640 - 4200)	1531 (592 - 4400)	p = 0.85
Birth length (cm)	41 (32 - 57)	41 (30 - 55)	p = 0.95
Gestation (weeks)	31 (25 - 42)	31 (25 - 42)	p = 1.0
M:F	52:54 (49%:51%)	67:37 (64%:36%)	p = 0.035
Antenatal steroids	22 (21%)	30 (29%)	p = 0.231
Initial Crs	1.5 (0.5 - 7.9)	1.5 (0.6 - 5.6)	p = 0.78
Inborn	94 (89%)	96 (92%)	p = 0.509
Delivery mode			
Vaginal	52 (49%)	47 (45%)	
C/S in labour	20 (19%)	25 (24%)	
C/S no labour	34 (32%)	32 (31%)	p = 0.654
Singleton	86 (81%)	83 (80%)	p = 0.946
Apgar at 1 minute	5 (0 - 9)	5 (0 - 9)	p = 0.45
Apgar at 5 minutes	8 (0 - 9)	8 (1 - 9)	p = 0.85

Adverse clinical events: The numbers of infants in each group with each adverse clinical event are given in table 3.8. Again there were no significant differences between the two groups for any individual adverse event or in the total number of infants in each group with any adverse event.

Table 3.8: Frequencies of adverse events. Data are number (%).

	Control Group	Experimental group	
n	106	104	
Vent. dependent on day 15	25 (24%)	18 (17%)	p = 0.339
O_2 dependent at 36 weeks	24 (23%)	19 (18%)	p = 0.539
Pneumothorax	8 (8%)	5 (5%)	p = 0.591
PIE	7 (7%)	3 (3%)	p = 0.331
Pulmonary haemorrhage	5 (5%)	1 (1%)	p = 0.214
Abnormal USS at 6 weeks	11 (10%)	15 (14%)	p = 0.496
Any adverse event	39 (37%)	36 (35%)	p = 0.853

Duration of ventilation: Surviving infants in the experimental group required respiratory support by endotracheal tube for a median (quartile) 3 (2-8) days compared to 5 (2-13) days for the controls (p = 0.03). The total duration of ventilation was 775 days for the infants in the experimental group and 1269 days for the controls. The median (quartile) ages in days at final extubation were 4 (2-10) for the experimental group and 5 (2-21) for the controls (p = 0.048).

Oxygen supplementation: Data on oxygen supplementation are presented in table 3.9. There were no significant differences between surviving infants in the two groups in duration of requirement for greater than 40% oxygen or in duration of requirement for any supplemental oxygen.

Table 3.9: Duration of oxygen supplementation in survivors. Data are median (quartile).

	Control group	Experimental group	
n	106	104	
Days in > 40% oxygen	2 (1 - 8)	2 (1 - 4)	p = 0.54
Days in oxygen	6 (3 - 43)	6 (2 - 35)	p = 0.33

Surfactant treatment: Details of the surfactant treatment received by surviving infants are shown in table 3.10. There were no significant differences in the number of infants in each group that received surfactant, the surfactant regimens used or the total number of surfactant doses administered to each group.

Table 3.10: Surfactant administration. Data are number (%).

	Control Group	Experimental Group	
n	106	104	
Received surfactant	53 (50%)	44 (42%)	p = 0.327
High dose Curosurf	8	6	
Low dose Curosurf	14	12	
Exosurf	31	26	p = 0.979
Total doses	100	87	

Other outcomes

Remaining outcome data are detailed in table 3.11. There were no significant differences between the two groups in the frequencies of development of chronic lung disease (defined as requiring supplemental oxygen and having an abnormal chest x-ray at 28 days of age), or persistent ductus arteriosus (requiring clinical intervention). Similar numbers of infants in the two groups were treated with steroids and intralipid. There were no differences in the patterns of cranial ultrasound abnormalities during the first week of life. The median duration of hospitalisation was almost identical for the two groups.

Table 3.11 Other study outcomes. Data are median (quartile) or number (%).

	Control Group	Experimental Group	
n	106	104	
CLD	29	23	p = 0.471
Steroids for CLD	22	17	p = 0.520
Significant PDA	27	16	p = 0.101
Given intralipid	42	35	p = 0.451
Abnormal USS week 1	25	23	p = 0.929
Subependymal bleed	8	10	
Intraventricular bleed	10	8	
Periventricular bleed	6	1	
Other USS abnormality	1	4	p = 0.125
Days in hospital	47 (25 - 75)	46 (24 - 68)	p = 0.79
Sum days in hospital	6101	5702	

Secondary analysis - non survivors

The characteristics of the infants that died are detailed in table 3.12. Again there were no significant differences between the groups in birth weight, gestational age, gender distribution or Crs at study entry. The experimental group contained a larger number of infants that had been delivered by elective Caesarian section.

Table 3.12: Patient characteristics (non-survivors). Data are median (range) or number (%).

	Control group	**Experimental group**	
n	16	19	
Birth weight (g)	838 (580 - 5250)	967 (452 - 1326)	p = 0.71
Birth length (cm)	35 (30 - 55)	34 (29 - 41)	p = 0.73
Gestation (weeks)	26 (23 - 39)	27 (25 - 31)	p = 0.15
M:F	10:6 (63%:37%)	12:7 (63%:37%)	p = 0.756
Antenatal steroids	4 (25%)	3 (16%)	p = 0.799
Initial Crs	1.1 (0.6 - 5.8)	1.0 (0.5 - 1.8)	p = 0.22
Inborn	12 (75%)	14 (74%)	p = 0.765
Delivery mode			
Vaginal	11 (69%)	8 (42%)	
C/S in labour	2 (13%)	1 (5%)	
C/S no labour	3 (18%)	10 (53%)	p = 0.005
Singleton	13 (81%)	16 (84%)	p = 0.827
Apgar at 1 minute	2 (0 - 9)	5 (1 - 9)	p = 0.10
Apgar at 5 minutes	7 (2 - 9)	8 (1 - 9)	p = 0.36

Adverse clinical events: The numbers of infants in each group with each adverse clinical event are given in table 3.13. Again there were no significant differences between the two groups for any individual adverse outcome.

Table 3.13: Frequencies of adverse events. Data are number (%).

	Control Group	Experimental group	
n	16	19	
Vent. dependent on day 15	2 (13%)	6 (32%)	p = 0.18
O_2 dependent at 36 weeks	0 (0%)	4 (21%)	p = 0.157
Pneumothorax	3 (19%)	4 (21%)	p = 0.799
PIE	5 (31%)	7 (37%)	p = 0.992
Pulmonary haemorrhage	5 (31%)	6 (32%)	p = 0.730
Abnormal USS at 6 weeks	3 (19%)	4 (21%)	p = 0.799

Duration of ventilation: Non-surviving infants in the experimental group received respiratory support by endotracheal tube for a median (quartile) 8 (3-27) days compared to 3 (1-12) days for the controls (p = 0.10). The total duration of ventilation was 411 days for the infants in the experimental group and 160 days for the controls.

Oxygen supplementation: Data on oxygen supplementation are presented in table 3.14. There were no significant differences between non-surviving infants in the two groups in duration of requirement for greater than 40% oxygen or in duration of requirement for any supplemental oxygen.

Table 3.14: Duration of oxygen supplementation. Data are median (quartile).

	Control group	Experimental group	
n	16	19	
Days in > 40% oxygen	3 (1 - 12)	5 (2 - 13)	p = 0.26
Days in oxygen	3 (1 - 9)	7 (3 - 27)	p = 0.09

Other outcomes - non survivors

Remaining outcome data are detailed in table 3.15. There were no significant differences between the two groups in the frequencies of development of chronic lung disease (defined as requiring supplemental oxygen and having an abnormal chest x-ray at 28 days of age), or persistent ductus arteriosus (requiring clinical intervention). Similar numbers of infants in the two groups were treated with steroids and intralipid. There were no differences in the patterns of cranial ultrasound abnormalities during the first week of life. The median duration of hospitalisation was almost identical for the two groups.

Table 3.15: Other outcomes (non-survivors). Data are median (quartile) or number (%).

	Control Group	Experimental Group	
n	16	19	
CLD	2 (13%)	3 (16%)	p = 0.835
Steroids for CLD	1 (6%)	3 (16%)	p = 0.726
Significant PDA	3 (19%)	2 (11%)	p = 0.835
Given intralipid	5 (31%)	13 (68%)	p = 0.064
Abnormal USS week 1	10 (63%º	11 (58%)	p = 0.945
Subependymal bleed	1 (6%)	1 (5%)	
Intraventricular bleed	5 (31%)	5 (26%)	
Periventricular bleed	4 (25%)	4 (21%)	
Other abnormality	0 (0%)	1 (5%)	p = 0.812
Days survived	6 (2-20)	7 (2-29)	p = 0.39
Sum days survived	210	465	

Discussion

In this study the introduction of measurements of static respiratory system compliance into clinical practice had no significant effect on any of the primary outcome measures. This disappointing estimate of the potential "real life" impact of respiratory function testing on the outcomes of a population should lead to caution in the rapidity with which it is being incorporated into routine care.

There are many possible reasons that no clinical benefit was demonstrated in this study. The obvious possibility is that there is no benefit. Many experiences during the study were against this conclusion in that in individual circumstances the data was often extremely helpful. There are already studies demonstrating specific areas of utility for the technology. Static Crs measurements correlate with gas exchange [191,203] and reflect the course of lung disease [14]. They may help select infants for surfactant treatment [63] and predict the likelihood of successful extubation [64]. Improvements in Crs are seen after surfactant treatment that are not apparent when dynamic measurements are used [15,160,204]. Crs predicts death from respiratory failure at least as well as other more traditional measures of disease severity [59,60]. The other information obtained using the single breath technique may also be useful. Measurements of respiratory system resistance (Rrs) can demonstrate endotracheal tube obstruction with secretions [16]. They can also demonstrate response to bronchodilators in infants with chronic lung disease [198,199]. The time constant could be used to ensure that the ventilator settings do not result in inadvertent PEEP [13].

Perhaps the potential benefit from the data is smaller than was hoped at the outset and a much larger sample size would be needed to demonstrate it clearly. Smaller improvements in outcome would still be important in a global sense but the cost of the technology would make it unattractive to clinicians making difficult resource decisions if it were unlikely to make a palpable difference to their own practice.

In the era of antenatal steroids and replacement surfactant only a small proportion of infants present serious problems with ventilation and it may be that by considering all ventilated infants the power of the study was blunted by the number of infants who were destined to have good outcomes in any case. Again a much larger sample size would be required to gather enough data for meaningful sub-group analysis.

The measurements were made daily and sometimes more frequently but perhaps this was not often enough. Without dedicated staff trained in the technique it would be impracticable for any sizeable neonatal unit to make more frequent measurements using the single breath technique because of the time involved and expertise required. The large number of studies that were unsuccessful is likely to have diminished the power of the study. This problem is unavoidable with the single breath technique but may be overcome with on-line techniques. Monitoring techniques that constantly display real time data on-line are becoming available [205]. It may be that these will solve that problem but they need to be critically evaluated because they will increase the respiratory dead space of the infant, often by several millilitres, and unless there is a reasonable leak around the endotracheal tube this will result in a need for more ventilation to achieve the same carbon dioxide exchange [84,85]. Because they make measurements under dynamic conditions they may be subject to all of the problems associated with this approach such as frequency dependence and distortion of the results by the effects of positive end-expiratory pressure. Kelly et al were unable to detect improvements in dynamic compliance and by inference tidal volume in a population of infants treated with Survanta despite large improvements in static compliance measured simultaneously using the single breath technique that were coupled with obvious clinical improvements [15].

Although the measurement results were written on the blood gas sheets along with an explanation of their significance the study did not stipulate that the medical staff caring for the infants acted on the basis of the study recommendations. At the time of the study these monitoring techniques were new to the majority of the staff and there was significant uncertainty about the reliability of the information. It may be that if the study was repeated now that the technique is accepted and understood that a different result would be obtained. We chose to present the data in the form of respiratory system compliance. This is an abstract concept that does not immediately mean anything quantifiable. It is possible that it would have been more meaningful to present tidal volume and expiration time data and to have asked the clinicians to set the ventilators so as to avoid excessive inflation volumes or inadequate expiration times.

If compliance measurement is a truly effective intervention it might be expected to result in the survival of some infants who would otherwise have died or prolonged the survival of some infants that eventually died. This might have blunted the power of the study. This sort of observation has been made with surfactant treatment and antenatal steroids [24]. There was by chance significant excess of males in the experimental group than in the control group. Males are known to have worse outcomes than females for a given birthweight or gestational age because of their increased severity of RDS [206]. This could have been avoided by stratifying randomisation by gender as well as by centre. When a secondary subgroup analysis of the results was performed according to whether or not infants survived there was a significant difference between the two groups in the duration of ventilation of surviving infants with infants in the control group requiring a median (quartile) of 5 (2-13) days ventilation compared to 3 (2-8) days for surviving infants in the experimental group ($p = 0.03$). The total duration of ventilation in survivors in the experimental group was roughly 40% less than that of controls.

This was not a pre-specified outcome and should be regarded as a hypothesis rather than a definitive finding. Any potential advantage in survivors would be offset by the longer survival that was observed in the infants that eventually died that were in the experimental group.

There are no other published trials of this nature for direct comparison. Rosen et al [111] performed a retrospective comparison of their outcomes during two consecutive time periods during the second of which they instituted regular pulmonary function testing into routine care. They found a lower incidence of pneumothoraces and intraventricular haemorrhages in the second group. The pulmonary function testing was performed frequently by three senior neonatologists and repeated whenever the ventilator settings were adjusted. It may be that the increased frequency of measurement enabled a greater effect or that the increased frequency of assessment by a senior neonatologist alone would have been effective. It may also be that the expertise of the clinicians had improved by the second time period. This study was performed in the pre-surfactant era when outcomes may have been more dependent on ventilator management than now.

The way that health care is currently structured in the UK means that the majority of the routine neonatal ventilation is managed by Senior House Officers and Registrars with relatively little experience that change post every six months. They are supervised by senior Neonatologists who educate them whilst in post but there is probably a limit to the amount of information about sophisticated ventilation techniques and detailed respiratory physiology that they can be expected to learn and use effectively in such a short time. Emphasis should be therefore be placed on simple effective concepts. Information overload is likely to be counterproductive. Improvements in outcomes are likely to require changes in the structure of care which place the patients more constantly in the hands of more experienced personnel.

In the meantime new technology such as this is only likely to be palpably effective if it combines useful information with an effective, simple information display that encourages its use. We have been unable to demonstrate that this is the case for the single breath technique for measuring static respiratory system compliance. Further research is urgently required to evaluate other techniques before they become irreversibly incorporated into practice.

Chapter 4: Reproducibility of Respiratory System Compliance Measurements

Introduction

Before any technique for measuring a physiological variable is introduced into clinical practice with the potential to alter clinical decisions there should be a clear understanding of the accuracy and reproducbility of the data generated. There are no clearly agreed standards of accuracy or reproducibility for respiratory system mechanics measurements in ventilated newborn infants nor are there agreed methods for assessing it [139]. Different authors have used a variety of methods to determine this within their studies. In practical terms the acceptable reliability standards of a method depend on the circumstances of its use. If any accidental difference between two successive measurements performed in close succession were large enough to be confused with a clinically relevant change that might influence management then this would be important. Having stipulated the data acceptance criteria described in the opening chapter we studied various aspects of the reliability of the methodology.

Intra-observer reliability

Patients and methods

To assess the intra-observer reliability of the technique, paired Crs measurements were made 5 minutes apart in a group of ventilated infants treated with surfactant for respiratory distress syndrome. Three hours after exogenous surfactant was given endotracheal suction was performed.

Five minutes later a series of breaths were sampled. The apparatus was then removed from the ventilator circuit for 5 minutes and then re-inserted for a further measurement series. The results of the 2 studies were then analysed and compared.

To obtain 25 successful paired Crs measurements 32 infants were studied. Paired results were not obtained in 7 infants. In 4 of these 7 infants both attempts at measurement were unsuccessful because of inability to induce satisfactory respiratory muscle relaxation in active infants. In 1 infant 1 of the 2 measurements was unsuccessful because of the same reason. In 1 infant 1 of the 2 studies was unsuccessful because of insufficient linearity of the flow-volume relationship and in 1 infant both studies were unsuccessful because of an air leak around the endotracheal tube that could not be eliminated. The characteristics of the infants with successful measurements are detailed in table 4.1.

Results

The results of the paired Crs measurements are shown in table 4.2 and displayed graphically in figures 4.1 and 4.2. There was no systematic difference between the pairs in either direction. The absolute size of the potential error did not vary with the mean compliance so the percentage error was a little larger the lower the underlying compliance. 95% of all paired measurements would be expected to be within 0.2 $ml/cmH_2O/m$ of one another or within 15% of one another (mean difference ± 2 sd) [195].

Table 4.1: Characteristics of the infants in the intra-observer reliability study.

Infant no.	Gestation (weeks)	Birth weight (g)	Length (cm)
1	30	976	37
2	30	1340	41
3	31	1837	43
4	29	1618	43
5	34	2330	46
6	35	2660	49
7	31	1793	42
8	32	2070	40
9	29	1396	39
10	29	990	37
11	29	1785	42
12	30	1508	43
13	27	1010	35
14	28	825	34
15	27	900	35
16	25	945	35
17	29	1390	37
18	29	1380	41
19	31	1710	43
20	35	2500	48
21	28	958	35
22	27	755	34
23	31	1595	41
24	29	1430	40
25	26	1020	38
Mean (range)	30 (25-35)	1469 (755-2660)	40 (34-49)

Table 4.2: Paired Crs results (ml/cmH_2O/m).

Infant no	Crs 1	Crs 2	Mean	Difference	% Difference
1	1.0	0.9	0.95	0.1	10.5
2	2.0	2.0	2.0	0	0
3	1.1	1.1	1.1	0	0
4	1.4	1.4	1.4	0	0
5	1.2	1.2	1.2	0	0
6	0.8	0.8	0.8	0	0
7	1.7	1.6	1.65	0.1	6.1
8	1.6	1.6	1.6	0	0
9	1.7	1.7	1.7	0	0
10	1.1	1.2	1.15	-0.1	-8.7
11	1.2	1.1	1.15	0.1	8.7
12	1.3	1.1	1.2	0.2	16.7
13	0.9	0.9	0.9	0	0
14	1.0	1.0	1.0	0	0
15	0.9	1.0	0.95	-0.1	-10.5
16	1.2	1.3	1.25	-0.1	-8
17	1.3	1.3	1.3	0	0
18	1.1	1.2	1.15	-0.1	-8.7
19	2.2	2.0	2.1	0.2	9.5
20	1.7	1.7	1.7	0	0
21	0.8	0.9	0.85	-0.1	-11.8
22	1.0	1.0	1.0	0	0
23	1.7	1.6	1.65	0.1	6.1
24	1.2	1.1	1.15	0.1	8.7
25	2.0	2.0	2.0	0	0
Mean (sd)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	0.016 (0.085)	0.74 (7)%

Figure 4.1: Difference between paired measurements of Crs plotted against the mean of the two measurements. Dotted lined indicate ± 2 sd of the difference.

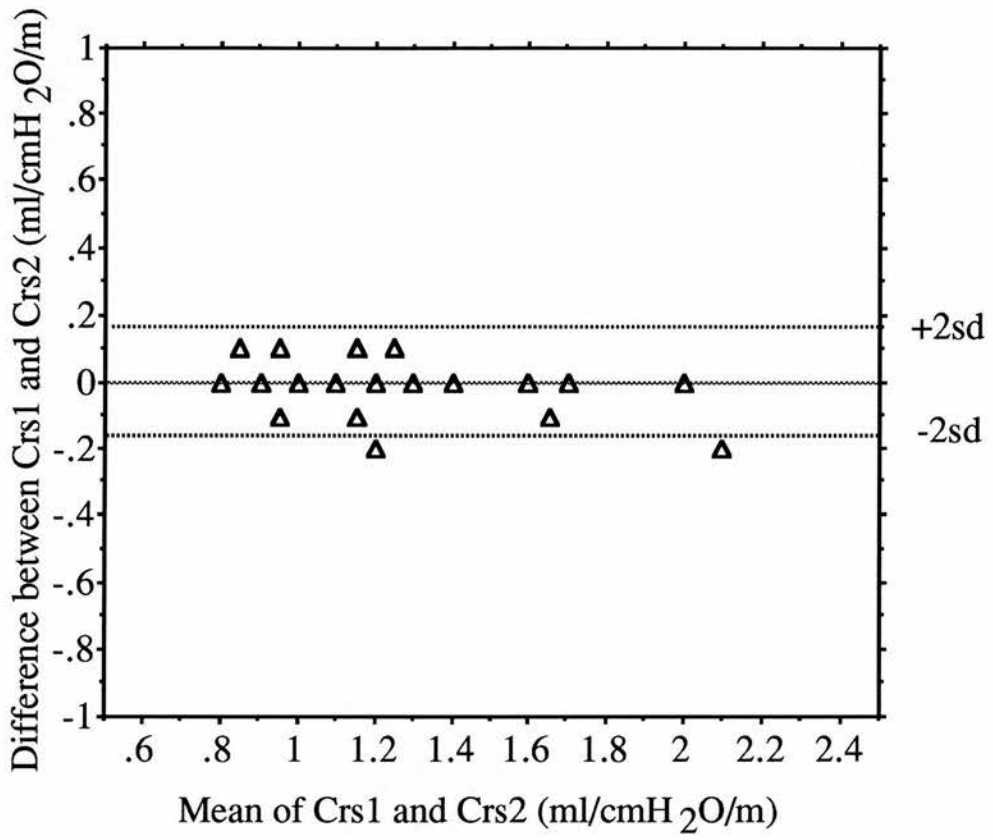
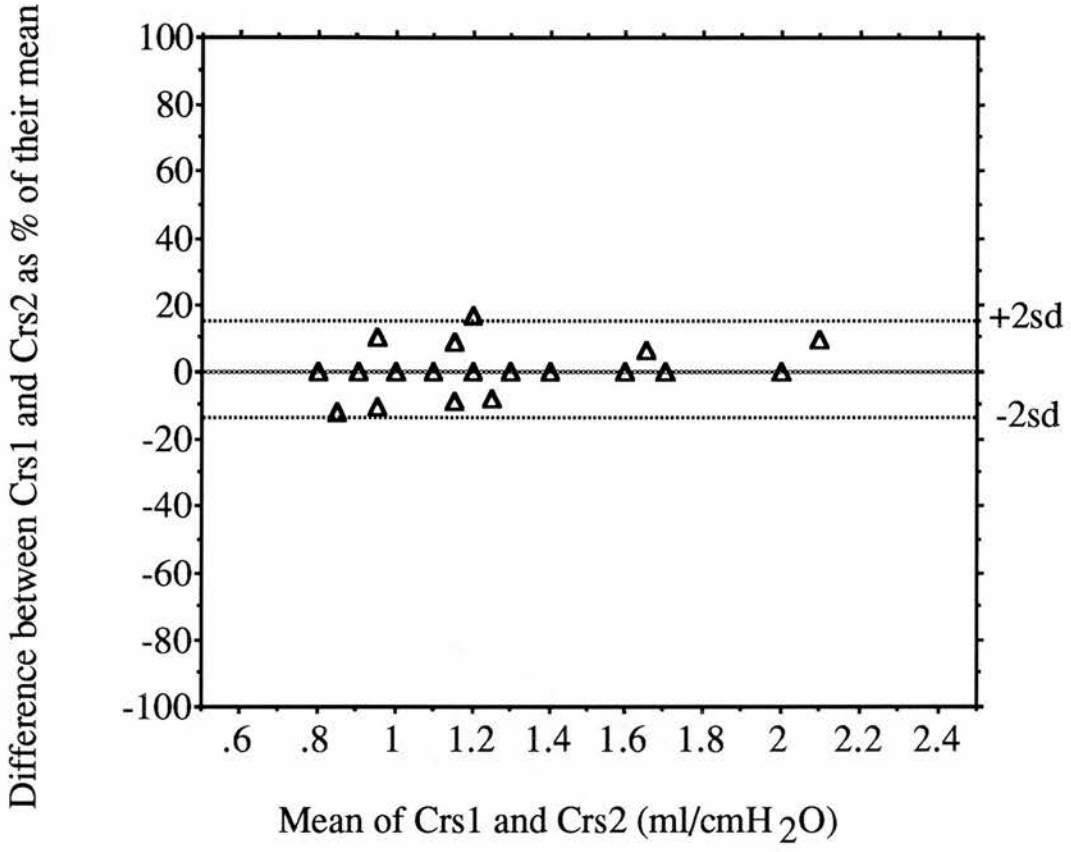


Figure 4.2: Difference between paired measurements of Crs as % of their mean plotted against the mean of the two measurements. Dotted lined indicate ± 2 sd of the difference.



Inter-observer reliability

Patients and methods

The Crs results for all of the studies described in this thesis were calculated using the same criteria as described in chapter 1. When analysing the data from a single measuring session on a single patient the observer selects the satisfactory breaths and then manually selects the linear portion of the flow-volume trace that will be used to determine the time constant for each breath. The final result is calculated as the average of the results of all the satisfactory breaths. Although breath acceptance criteria were defined it was possible that two observers independently reviewing the same dataset might accept or discard different breaths. If they also selected different portions of the flow-volume plots for analysis then they might obtain quite different results despite analysing the same dataset. To determine the possible magnitude of this problem as it related to our study, 10 infants from each centre that were enrolled in the randomised controlled trial of Crs measurements were selected by the generation of random numbers. The stored data from the first 5 studies performed on each infant (or all the studies performed on that infant if there were fewer than 5) were retrieved and re-analysed by the observer from the other centre, blind to the results obtained from the initial analysis.

The characteristics of the infants whose data were assessed are detailed in table 4.3. Their range of birthweights and body lengths spanned the whole study population although the mean values for these parameters were higher than those for the study as a whole. Between them there were 71 studies for which satisfactory data were obtained.

Table 4.3: Patient characteristics for inter-observer reliability study.

Study Number	Length (cm)	Weight (kg)	No. of Studies
N2	46	2.40	4
N7	50	3.03	4
N12	33	0.74	4
N15	37	1.30	5
N26	48	2.46	4
N34	42	1.62	5
N35	43	2.26	2
N40	49	3.00	4
N42	45	2.02	1
N44	36	1.02	4
S18	43	1.62	2
S19	44	2.35	1
S32	47	2.81	4
S46	37	1.03	5
S49	41	1.60	2
S50	34	0.80	5
S57	44	1.74	4
S89	47	2.09	4
S92	45	2.22	2
S124	41	1.44	5
Mean (range)	43 (33-50)	1.88 (0.74 - 3.03)	Total 71

Results

There was no systematic bias in either direction between the 2 investigators. The mean (sd) difference between the results obtained by each observer was 0 (0.12 ml/cmH_2O/m) or 0 (7.4%). The range of differences was -0.3 to + 0.6 ml/cmH_2O/m (-15% - +32%). Statistically, 95% of differences between the 2 observers would be expected to lie between ± 0.25 ml/cmH_2O/m or between ± 15% (mean ± 2 sd). The full results are displayed in figs 4.3 and 4.4.

Fig. 4.3:Difference between paired values plotted against mean of paired values. Dotted lines represent ± 2 sd of the mean difference.

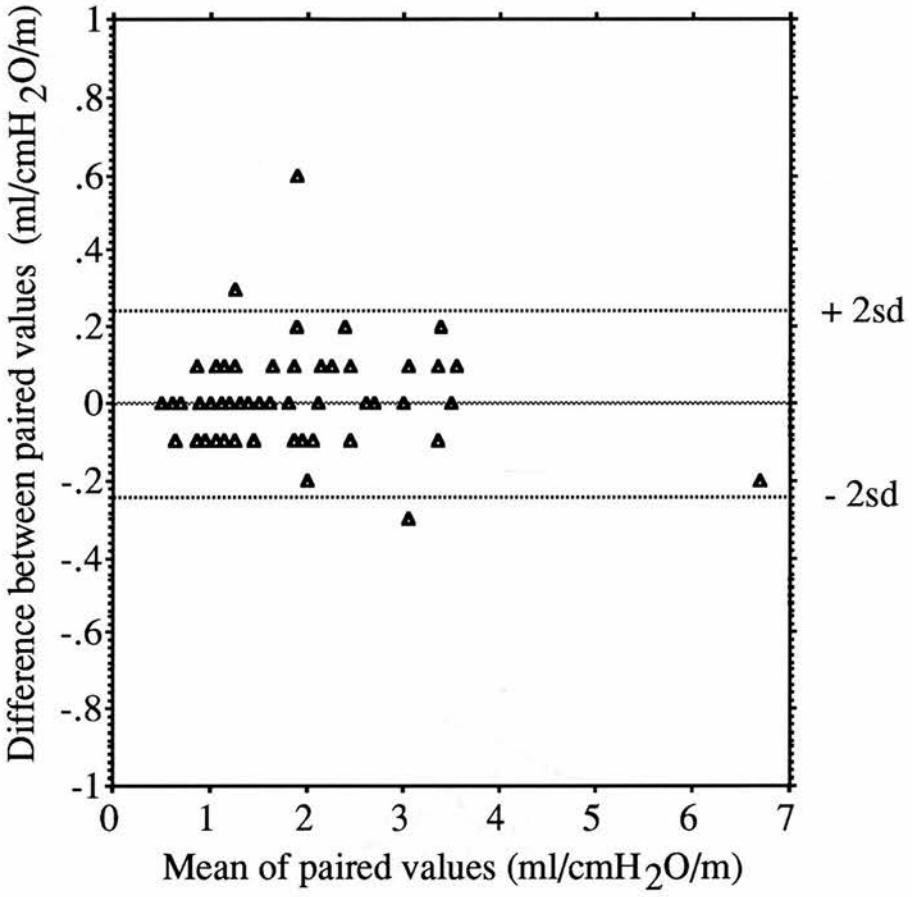


Figure 4.4: Difference between paired values expressed as % of their mean. Dotted lines represent ±2sd of the mean % difference.

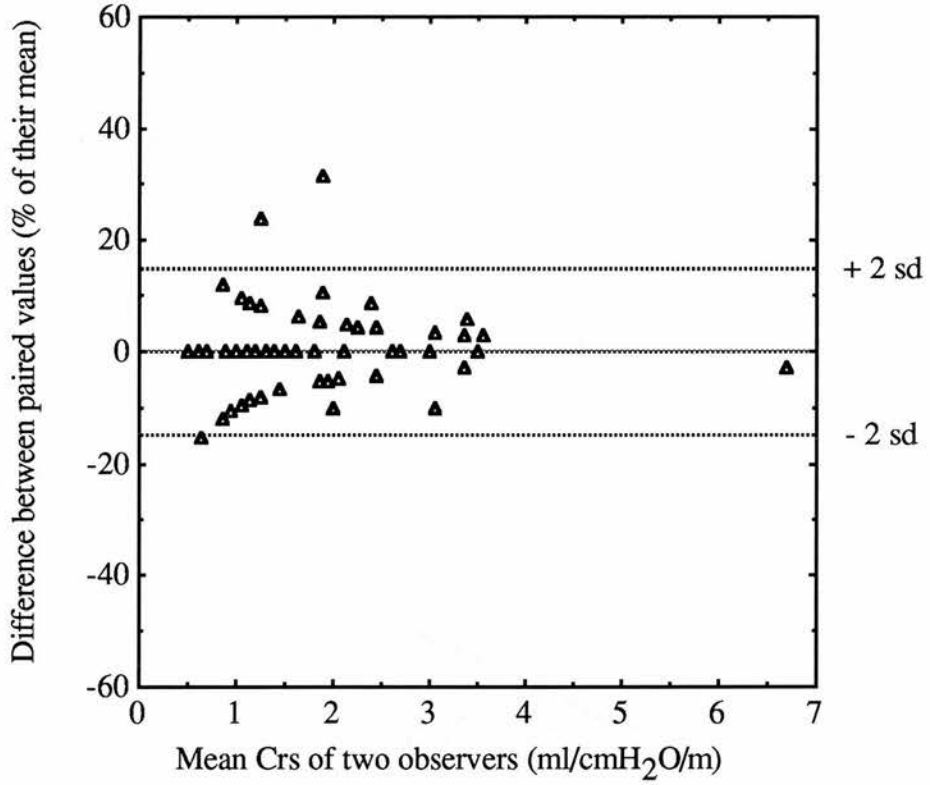


Figure 4.3 demonstrates that there was no change in the absolute size of the potential error associated with different observers analysing the same data in relation to the size of the underlying value for Crs. This means that the percentage potential error is larger the lower the underlying Crs as seen in figure 4.4.

Within study coefficient of variation

One of the data acceptance criteria in these studies was that the coefficient of variation of the results of individual breaths within a study should be less than 15%. This was imposed as a means of preventing the acceptance of potentially misleading data where respiratory muscle activity or non-linearity of the flow volume trace might influence the results. This would obviously be expected to result in an average coefficient of variation for each study that appeared favourable.

The mean (sd) within-study coefficient of variation between breaths for the last 227 sequentially performed successful studies within the randomised controlled trial of Crs measurements was 6.12 (3.54) % with a range of 0.43% to 14.67%.

Discussion

The data on intra- and inter-observer reliability indicate that the single breath technique as applied in these studies is acceptably reproducible. The data can only be assumed to apply to the population of infants studied under the conditions employed and for the rules for data screening applied. If less stringent rules were applied the variation in results would be expected to be wider.

As well as variations attributable to the methodology itself there are other sources of potential variation that need to be controlled between measurements Changes in infant position or ventilator settings are known to alter respiratory function test results [87,88,164,165,166,167,168]. The duration of the airway occlusion may also be important [117]. As discussed earlier the pressure-volume history of the lungs prior to the measurement may be important.

Infants recovering from RDS were selected for the comparison as they were generally still receiving fast enough ventilation to make them easy enough to study twice in quick succession. They therefore represent a population of infants in whom the reproducibility is likely to be better than average. Infants on low rate ventilation often become active towards the end of a study making a repeat study unlikely to be successful. This problem could have been overcome by sedating the infants but this was felt to be unjustifiable simply for the purpose of this study. The second study could have been performed several hours later or several repeat studies could have been performed over a period of hours but this would have introduced the possibility that some of the variation between the studies was due to true changes in the lung mechanics. Stable infants without lung disease could have been studied to overcome this problem but they would not have been relevant to the application of the technique in these studies as the study population consisted exclusively of ventilated infants.

The Crs results in all of the studies were expressed rounded to 1 decimal place after correction to body length as it was felt that changes smaller than this were clinically irrelevant. This could in small samples lead to under- or over-estimation of the repeatability of the measurement but should not have made a systematic difference in any one direction over the study as a whole. The potential errors between observers and measurements over time are small in relation to the range of Crs measurements between the severely stiff lungs of RDS and normal lungs.

Ideally the studies would have included an assessment of the variation between 2 measurements made in rapid succession in the same infants by different observers. Given the small number of infants in either centre that were enrolled in the study at any given time this was not feasible because of the travelling between centres that would have been involved but this would be an important area for further study. There are no published data examining this aspect of reproducibility of the single breath technique.

Obviously the data on the within study coefficient of variation are only as good as the 15% limit set on data acceptability and would be wider if these limits were relaxed. They are comparable to other similar data on the subject. Baraldi et al [160] found a median (range) coefficient of variation of 8.5 (2-17)% in 20 ventilated infants with RDS using the single breath technique. They did not report failure to obtain satisfactory data on any of their study infants at any time point in their study. Guslits et al [136] found a mean (range) within study coefficient of variation of 8.4 (1.9 - 14.3)% in 10 ventilated infants. Morley et al [190] using a sustained inflation method for measuring Crs found a within subject coefficient of variation of 22% for 6 measurements over 6 hours in 20 infants with RDS and attributed the variability to the long time period of their study. The infants had received surfactant and true changes in the lung mechanics might be expected over this time course. Thomson et al [137] found a between study coefficient of variation of 14% for Crs measured in 11 ventilated infants using the multiple occlusion technique. Fletcher et al [152] found the mean (range) change in Crs value on repeated measurement to be -1.3% (-4.9 - +4.7)% in 4 paralysed infants measured using the multiple occlusion technique under constant volume conditions but that increasing the tidal volume could lead to dramatic differences in the results obtained.

Mallol et al [116] found a within test coefficient of variation of 8.7 (4.3 - 16.4)% and a between test coefficient of variation of 11.9 (5-24.1)% when they studied spontaneously breathing infants recovering from bronchiolitis. Marchal et al [207] studied reproducibility of Crs measurements in 5 spontaneously breathing infants and found a mean (sd) within study coefficient of variation of 7.2 (3%) and a correlation coefficient of r=0.97 between paired measurements made 15-30 minutes apart in the same subjects. Haouzi et al [114] found a mean (sd) within subject coefficient of variation of 9.6 (5.3)% in spontaneously breathing infants. Popow et al [208] found a mean (sd) coefficient of variation of 3.9 (3)% using an occlusion technique in 10 spontaneously breathing infants.

The reproducibility of the single breath techniques as employed in the studies appears to compare reasonably to that observed by other authors using the same or similar techniques. Other authors have compared the reliability of static to dynamic compliance measurements and have generally found static measurements to be more reproducible[90,94,208,209] particularly when the dynamic measurement methodology incorporates the measurement of oesophageal pressure. The importance of controlling data quality for static techniques results in a significant number of episodes where measurements are attempted but are not successful. It may be that more relaxed criteria could be applied depending on the application intended for the results allowing greater success rate but further study would be required to ascertain whether it is safe to do so.

Chapter 5 : Changes in Respiratory System Compliance Following Treatment With Exogenous Surfactant.

Comparison of Curosurf and Exosurf

Introduction

Exogenous replacement surfactant has now become established as a routine treatment for infants with respiratory distress syndrome. In contrast to most treatments currently in use its introduction followed numerous well designed randomised controlled trials which have established its effectiveness beyond reasonable doubt, whether given prophylactically to infants at risk of RDS or as a rescue treatment for those with established disease. These have been well reviewed [19,20,210,211]. There are many different preparations, some artificial and some derived from animal lungs and there are potentially important biochemical differences between these preparations which might be expected to affect the way that they cause the lungs to behave following their instillation.

In the neonatal units of the Simpson Memorial Maternity Pavilion and Ninewells Hospital during the study period two surfactants were in use. Between July 1991 when the study began and December 1991 all infants treated with surfactant in both units received Curosurf. They were enrolled in Curosurf IV which was a randomised trial comparing the effectiveness of two dose regimens [201] that was already in progress at the time that these studies commenced.

The Curosurf trial ended at the end of December 1991 and from January 1992 until the end of the study period in June 1993 infants in both centres received Exosurf Neonatal which was at that time the only readily available licensed product in the United Kingdom. Curosurf is a preparation of polar lipids isolated from minced pigs lungs. It contains approximately 99% lipids, mainly phospholipids, and 1% low molecular weight hydrophobic apoproteins SP-B and SP-C [212]. Exosurf is a wholly synthetic surfactant which contains 13.5 mg/ml of dipalmitoyl phosphatidyl choline, 1.5 mg/ml hexadecanol, 1 mg/ml tyloxapol in 0.1N sodium chloride and no surfactant apoproteins [46].

In order for pulmonary surfactant to lower surface tension effectively its principal component dipalmitoylphosphatidylcholine (DPPC) must be able rapidly to form a surface film over the air-water interface in the airspaces of the lung. In the absence of the surfactant apoproteins, DPPC does this very poorly [213]. These apoproteins (SP-B and SP-C) are responsible for improving its characteristics in this respect. Surfactants derived from animal lungs such as Curosurf contain these apoproteins whereas artificial surfactants do not. The hexadecanol and tyloxapol in Exosurf are added to mimic the effects of the apoproteins. Measured in vitro the surface properties of the two surfactants are different, with Curosurf reducing surface tension more effectively [46,213,214,215,216]. Since RDS is caused by increased surface tension in the lung resulting from surfactant deficiency [217], it might be expected that the replacement surfactant with the greater ability to reduce surface tension would produce a more pronounced physiological effect. This is the case in animal models of RDS. Randomised studies have shown that naturally derived surfactants produce a larger, more rapid improvement in lung mechanics and oxygenation than artificial ones [46,213,215,216,218,219,220]. The position is less clear in human infants.

The early clinical response to exogenous surfactant therapy is variable, but there is usually a rapid improvement in oxygenation and a reduction in requirements for ventilatory support. At the time of our studies human infants had not been demonstrated to show consistent early changes in lung compliance after exogenous surfactant [86,172,188,189,190,221,222,223,224,225,226] although one study examining the effects of canine surfactant on lungs excised from human infants that had died from respiratory distress syndrome showed that it produced immediate improvements in the lung pressure-volume characteristics [227]. This inconsistency between the animal and human data was puzzling. It may have been a reflection of the methodologies used for measuring the lung mechanics and in the earlier studies the lack of activity of the surfactant preparations used or the administration technique.

We planned in our original protocol to study the changes in Crs, ventilation requirements and oxygenation seen following surfactant treatment in a randomised comparison of Curosurf and the artificial surfactant ALEC (artificial lung expanding compound). Unfortunately the Curosurf IV study ended before we had randomised any infants to ALEC, and Curosurf ceased to be available to us. We therefore started using Exosurf and continued to evaluate the acute effects of treatment as we had been doing. This chapter details the findings of our investigations. Although the results seen after the two surfactants are presented for comparison it must be stressed that surfactant allocation was not randomised so comparative interpretation should be cautious.

Patients and methods

All infants treated with surfactant in either centre that had been enrolled in the randomised controlled trial of Crs measurements were eligible for inclusion in this study. Infants were treated with surfactant if between 2 and 72 hours of age they required mechanical ventilation for clinical and radiological respiratory distress syndrome (RDS) and had an arterial/alveolar (a/A) oxygen tension ratio < 0.22. Oxygenation, ventilator support requirements and static respiratory system compliance (Crs) were assessed in each infant shortly before and 3 and 12 hours after the first dose of surfactant. All the infants were ventilated with Sechrist iv 100b pressure limited, time cycled, continuous flow ventilators. The investigators were not responsible for the clinical care of the infants. The study was accepted by the ethical committees of both hospitals. Written consent was obtained from one or both parents prior to the inclusion of their infant in the study.

Infants given Curosurf were randomly assigned to receive either 1.25 or 2.5 ml /kg body weight (100mg or 200mg/kg) as directed by the Curosurf IV randomisation centre. Half was delivered into each lung by positioning the infant on one side before instilling the surfactant intratracheally and continuing mechanical ventilation in that position for one minute. The procedure was then repeated on the opposite side. Infants given Exosurf received 5 ml/kg administered over approximately 20-30 minutes into a side arm of the proximal endotracheal tube. The infants remained supine and mechanical ventilation continued throughout. The Exosurf was given more slowly with the aim of minimising the risk of poor toleration of the larger volume in terms of decreased oxygenation and heart rate which was being experienced by others giving Exosurf more rapidly at the time [228].

Respiratory System Compliance measurements

Static respiratory system compliance (Crs) was measured using the computerised single breath passive expiratory flow technique as already described. Changes in Crs over the study period were expressed as percentage changes in relation to their corresponding pre-treatment value. Before analysis of the results, the infants were subdivided according to whether their static Crs before treatment was consistent with surfactant deficiency (<1.8 ml/cmH_2O/m) or surfactant maturity (≥1.8 ml/cm H_2O/m). This was based on two previous studies. D'Costa et al [229] measured lecithin/sphingomyelin (L/S) ratios using high performance liquid chromatography (HPLC) on directly sampled tracheal secretions from 115 newborn infants taken within 3 hours of birth. They found that this assay could predict respiratory distress syndrome requiring ventilation with 100% sensitivity and 91% specificity. Wilkie et al [63] applied this assay using identical equipment in two populations of ventilated newborn infants in whom they also measured Crs. They found that a static Crs of < 1.8 ml/cmH_2O/m predicted an immature tracheal aspirate L/S ratio with 93% sensitivity, 94% specificity, 96% positive predictive value and 89% negative predictive value. On this basis we wished to examine whether or not the degree of lung maturity apparent from the pre-treatment Crs as opposed to the clinical and radiological findings (which suggested RDS in all cases) influenced the response to surfactant treatment.

Oxygenation

Arterial oxygen tension (PaO_2) was measured intermittently by arterial puncture or sampling from arterial lines. Oxygenation was expressed as the fractional inspired oxygen concentration (FiO_2) required at the time of study to maintain the infants' arterial or transcutaneous PO_2 between 6 and 10.3 kPa or oxygen saturation between 90 and 94% by pulse oximetry. These limits were those in current use in the two nurseries as the desired range for ventilated newborn infants.

Ventilator support requirements

In order to adjust for variations in ventilator settings between infants, we used the ventilator efficiency index (VEI) devised by Notter et al [230] as an estimate of ventilation requirements. This index estimates alveolar ventilation in relation to ventilator input and can be calculated by the equation:

$$VEI = \frac{3800}{p \times f \times PaCO_2}$$

where p is the inspiratory pressure minus the expiratory pressure of the ventilator, f is the ventilator rate in cycles per minute and $PaCO_2$ is the arterial partial pressure of CO_2 in millimetres of mercury. VEI increases as ventilation becomes easier. As ventilation requirements become minimal VEI increases rapidly. Therefore all VEI values of >1 were defined as 1 in the group comparisons [231].

Data collection and statistical analysis

The results were analysed using SPSS-PC and Minitab. Variables were compared 3 and 12 hours after surfactant treatment to their corresponding pre-treatment value in paired group analyses using the Wilcoxon matched pairs signed ranks test. Comparisons of the distributions of variables between the two surfactants were made using the Mann-Whitney U test. A probability was accepted as statistically significant if $p<0.05$.

Results

During the study period 111 infants were treated with surfactant in the two centres and 88 of these infants were enrolled in this study (table 5.1). They did not differ from the whole population of 111 infants in terms of their basic characteristics. Pairs of Crs measurements were made successfully in 73 of these 88 infants (83%).

The reasons for failure to obtain Crs data in the others were (i) inability to obtain adequate pressure plateaux following airway occlusion (either because of air leaks around the endotracheal tube or failure to induce a Hering-Breuer reflex in active infants) or (ii) alinearity of the flow-volume relationship. Of the 15 enrolled infants without successful Crs measurements 9 received Curosurf and 6 Exosurf. There was no statistically significant difference in birth weight, gestational age or oxygen requirement before treatment between them and the babies measured successfully. Their changes in oxygen requirements and VEI after treatment were similar to those seen in the infants measured successfully that were treated with the corresponding surfactant.

Table 5.1: Infants eligible for study, enrolled and successfully measured. Gender, gestation, birth weight and length by surfactant. Data are expressed as median (range).

	Curosurf	Exosurf
Eligible	56	55
M/F	35/21	33 /22
Gestation (weeks)	29 (23-37)	30 (23-38)
Birth weight (g)	1253 (580-3250)	1370 (600-4150)
Enrolled	48	40
Gender M/F	31/17	26/14
Gestation (weeks)	29 (23-35)	29 (25-38)
Birth weight (g)	1226 (580-2540)	1285 (607-4150)
Measured	39	34
Gender M/F	26/13	21/13
Gestation (weeks)	29 (25-35)	29 (25-38)
Birth Weight (g)	1253 (677-2540)	1285 (607-4150)
Length (cm)	38 (32-39)	40 (33-52)

Of the 73 enrolled infants with valid Crs data, there were no differences in the distributions of birth weight, gestational age, oxygen requirement before treatment, Crs before treatment, and postnatal age at treatment between the infants treated with Curosurf and those treated with Exosurf (table 5.2). The infants with initial Crs suggesting surfactant deficiency (<1.8 ml/cmH_2O/m) who received Exosurf had slightly greater ventilation requirements (lower VEI) before treatment than those treated with Curosurf. There were 15 infants whose Crs values before treatment were not consistent with surfactant deficiency (≥1.8 ml/cmH_2O/m). They were significantly heavier, easier to ventilate, older at time of treatment and of later gestation than those whose initial Crs was consistent with surfactant deficiency.

The changes in Crs, oxygen requirements and VEI seen after treatment are shown in figures 5.1 and 5.2. Of the 58 infants with initial Crs < 1.8 mls/cmH_2O/m (fig 5.1) 32 received Curosurf. They showed a median improvement in Crs of 17.9 % (p=0.002) 3 hours after treatment increasing to 39.3 % (p=0.0001) at 12 hours. These changes were accompanied by significant improvements in oxygenation and VEI at both 3 and 12 hours. The 26 infants who received Exosurf showed no statistically significant changes in Crs at 3 or 12 hours with median changes of -6.2% (p = 0.24) at 3 hours and +5% (p = 0.28) at 12 hours. Their oxygen requirements were significantly lower at 3 hours than before treatment but their ventilation requirements were not improved until 12 hours. The median reduction in oxygen requirement was greater after Curosurf as compared to Exosurf both at 3 hours (change in FiO_2 -0.32 compared to -0.11; $p < 0.001$) and 12 hours (-0.32 compared to-0.13 ; $p < 0.005$) after treatment.

Table 5.2: Pre-treatment patient characteristics by surfactant and initial Crs. Data are median (range).

	Curosurf <1.8 ml/cmH_2O/m	Exosurf <1.8 ml/cmH_2O/m	Curosurf ≥1.8 ml/cmH_2O/m	Exosurf ≥1.8 ml/cmH_2O/m	All <1.8ml/cmH_2O/m	All ≥ 1.8 ml/cmH_2O/m
n	32	26	7	8	58	15
Gestation (weeks)	28 (25-35)	29 (25-38)	32 (28-35)	35 (25-37)	28 (25-38) †	32 (25-37) †
Birth weight (g)	1159 (677-2540)	1240 (607-4150)	1690 (1263-2460)	2840 (703-3600)	1195 (607-4150) ‡	2260 (703-3600)‡
Length (cm)	37 (32-47)	39 (33-52)	44 (37-49)	48 (34-51)	38 (32-52) ‡	46 (34-51) ‡
M/F	22/10	15/11	4/3	6/2	37/21	10/5
Age at first dose (decimal hr)	5.00 (2.35-37.20)	5.10 (3.15-50.80)	16.98 (3.63-53.50)	22.65 (5.13-41.32)	5.01 (2.35-50.8) †	16.98 (3.63-53.50)†
Initial Crs ml/cmH_2O/m	1.1 (0.6-1.6)	1.1 (0.5-1.7)	2.1 (1.8-2.6)	2.1 (1.8-2.7)	1.1 (0.5-1.7)	2.1 (1.8-2.7)
Initial FiO_2	0.68 (0.32-1.0)	0.73 (0.30-0.95)	0.60 (0.50-1.0)	0.63 (0.48-0.90)	0.70 (0.30- 1.0)	0.60 (0.48-1.0)
Initial VEI	0.13 (0.05-0.43) *	0.12 (0.08-0.26) *	0.19 (0.11-0.64)	0.16 (0.09-1.0)	0.13 (0.05-0.43) *	0.19 (0.09-.1.0) *

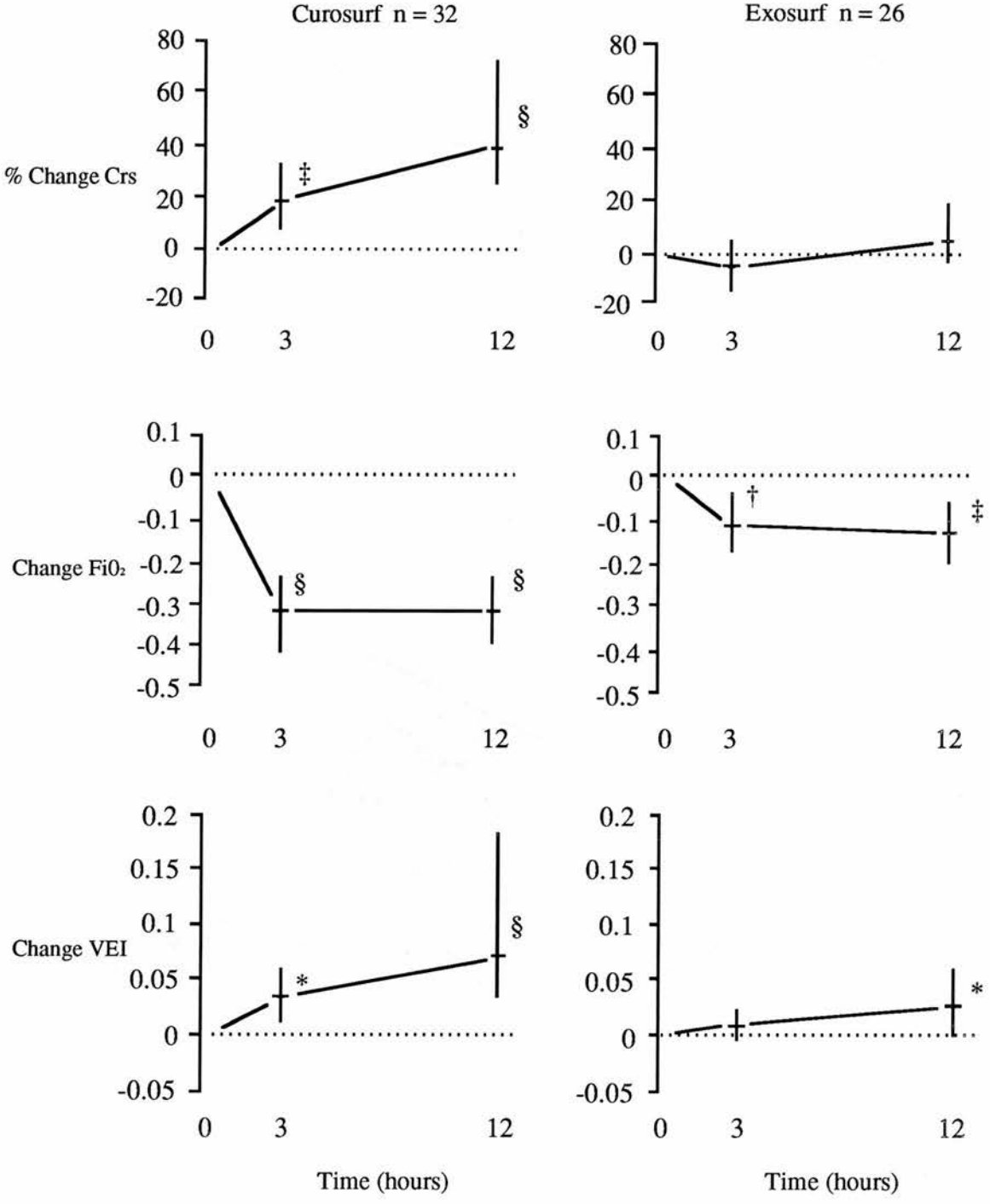
Symbols denote significant difference between groups (Mann-Whitney U).

* $p = < 0.05$, † $p = < 0.005$, ‡ $p = < 0.0005$.

If the Crs results of these infants are expressed in absolute terms rather than as percentage changes from the baseline Crs, the same pattern is observed with median pre-treatment Crs for the Curosurf treated infants of 1.1 ml/cmH_2O/m and median change at 3 hours of + 0.2 ml/cmH_2O/m (p=0.0037), and median pre-treatment Crs for the Exosurf treated infants of 1.1 ml/cmH_2O/m and median change at 3 hours of -0.1 ml/cmH_2O/m (p=0.156). At each time point in figure 5.1 the medians and 95% confidence intervals for each of the three variables were calculated from the same infants except that there was one missing data point for the VEI in an infant treated with Exosurf.

It was not our prestated intention to analyse the changes in the time constant (τ) or resistance of the respiratory system as part of this study. Nevertheless when the computerised single breath technique is used these are automatically derived. They are presented in table 5.3. There was a slight lengthening of τ after Curosurf (+ 0.0125 s at 3 hours and + 0.0215 s at 12 hours). This was not surprising given the increase in compliance seen in these infants. This would cause an increase in the time taken for 95% complete expiration (3τ) of 0.0375 s at 3 hours and 0.0645 s at 12 hours. The median time constant 12 hours after treatment with Curosurf was 0.083 seconds. Therefore unless the infant was receiving a high rate of ventilation, a change in the time constant of this magnitude would be unlikely to have important consequences such as inadvertent PEEP in the majority of cases. The slight shortening of the time constant after Exosurf, jointly attributable to a small fall in both compliance and resistance would result in a median decrease in the time taken for 95% complete expiration of 0.042 seconds which would be unlikely to be clinically important unless an infant was not receiving positive end expiratory pressure as part of the ventilation strategy. Both neonatal units in the study routinely use PEEP in all ventilated neonates.

Fig 5.1: Changes following surfactant administration in infants with initial Crs < 1.8 ml/cmH_2O/m. Graphs show medians with 95% confidence intervals.



Symbols denote significant difference from value before treatment. * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.005$, § $p = 0.0001$ (Wilcoxon matched pairs signed rank test).

Table 5.3: Changes in time constant (τ) and respiratory system resistance (Rrs) for infants with initial Crs < 1.8 ml/cmH_2O/m. Data are expressed as median (95% confidence intervals).

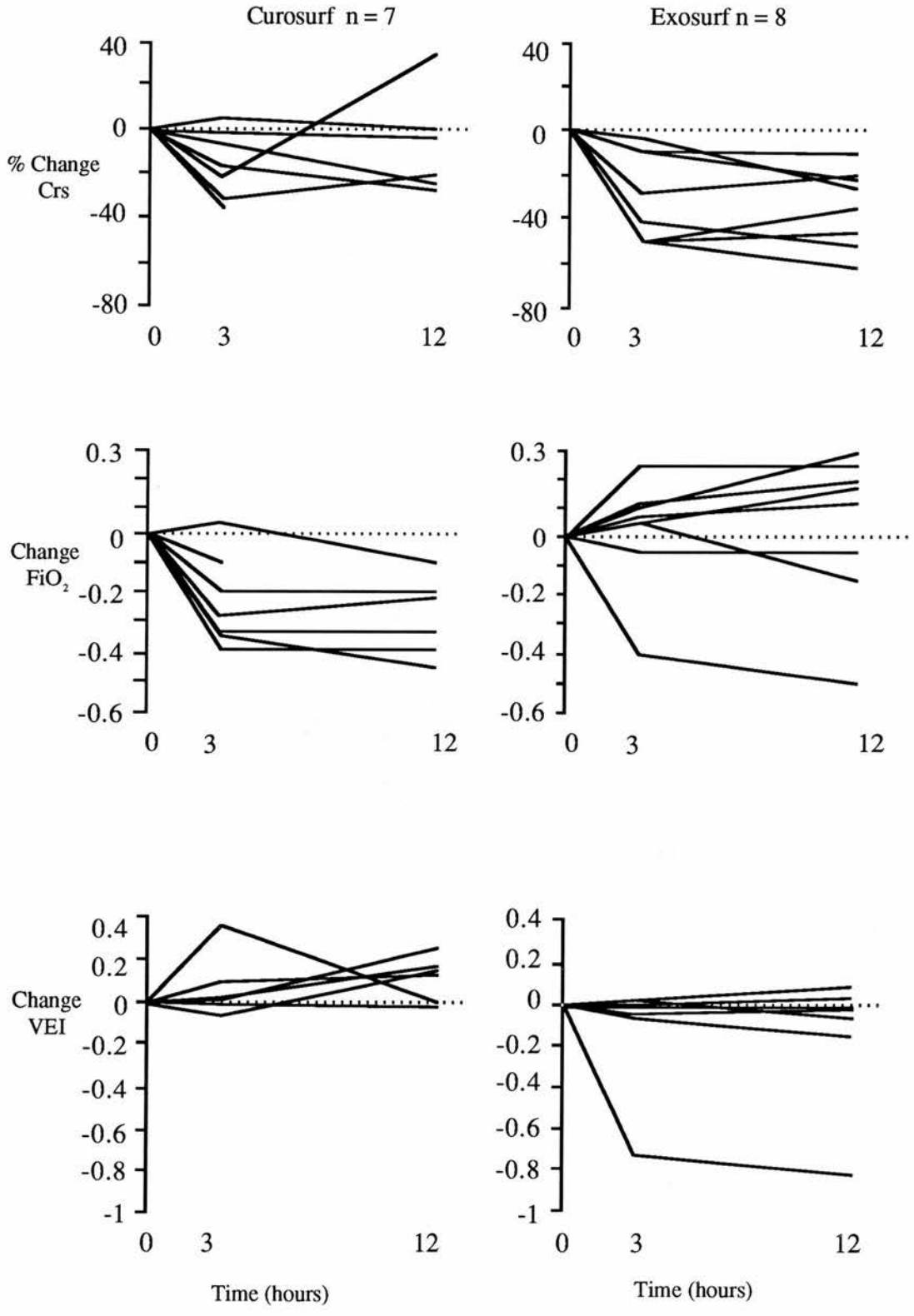
	3 HOURS				12 HOURS			
CUROSURF								
	n	**median**	**95% confidence intervals**	**p**	**n**	**median**	**95% confidence intervals**	**p**
Change τ (s)	32	0.0125	0.001, 0.021	0.033	30	0.0215	0.0105, 0.0415	0.0002
Change Rrs (cmH_2O/ml/s)	32	0	-0.015, 0.025	0.778	30	0.005	-0.015, 0.02	0.638
EXOSURF								
	n	**median**	**95% confidence intervals**	**p**	**n**	**median**	**95% confidence intervals**	**p**
Change τ (s)	25	-0.014	-0.03, -0.0035	0.005	25	-0.005	-0.0285, 0.0065	0.493
Change Rrs (cmH_2O/ml/s)	25	-0.02	-0.045, -0.01	0.001	25	-0.02	-0.055, 0	0.048

There were 15 infants with initial Crs suggesting a mature lung phospholipid profile ($\geq$ 1.8 ml/cmH_2O/m). Their results are presented in figure 5.2. All 8 treated with Exosurf and 5 out of 7 treated with Curosurf showed a fall in Crs after treatment. The infants treated with Curosurf showed an overall reduction in their oxygen requirements whilst those treated with Exosurf did not. There was no consistent pattern to their changes in VEI. After either surfactant there was a slight shortening of τ in association with the fall in Crs. The infants treated with Curosurf showed a slight increase in respiratory system resistance whilst those treated with Exosurf showed a slight decrease. The numbers of observations were small so they have not been subjected to statistical analysis.

Discussion

In this study infants with a clinical and radiological diagnosis of RDS and an a/A ratio <0.22 demonstrated rapid improvements in Crs, oxygenation and ventilation requirements after porcine surfactant if their initial Crs was consistent with surfactant deficiency. A similar group of infants showed no improvement in Crs, a smaller improvement in oxygenation and a slower reduction in ventilation requirements over the same time after treatment with a synthetic surfactant. These two groups were not randomly assigned so this comparison should be interpreted with caution. However, the results are consistent with those of randomised studies using animal models of RDS as described above. They are also consistent with the individual studies of changes in static Crs following naturally derived [15,160] and synthetic surfactants [191,232,233] in human infants that have been published since the current studies were started. Two recent comparisons of Survanta and Exosurf in human infants [234,235] showed similar differences in acute response patterns between the two surfactants in terms of oxygenation and ventilation to those in our study although they did not measure Crs. Improved pressure-volume characteristics may therefore be an important factor in the rapid clinical improvements seen after natural surfactant.

Fig. 5. 2: Changes following surfactant administration in infants with initial Crs ≥ 1.8 ml / cm H_2O / m. (Lines represent individual infants).



At the time of our studies, published in vivo studies had not shown rapid improvements in lung mechanics that would explain the immediate improvements in gas exchange seen in human infants after treatment with replacement surfactant [86,172,188,189,190,191,221,222,223,224,225,226]. Some of these studies were made on infants treated with synthetic surfactant [188,189,190,191,223] which may have slower effects on lung mechanics and oxygenation than natural surfactant as we and others have found[191,232,233]. Seven studies had considered infants treated with natural surfactants [86,172,221,222,224,225,226]. Only one of these had measured changes in static Crs using the single breath technique [226]. There were no improvements documented. It is hard to find a reason why their results differ from ours and the other two recently published studies using the single breath technique to measure the response to natural surfactant except that their infants were quite sick in terms of FiO_2 and mean airway pressure requirements and this has been associated with a blunted response to treatment [225]. The other six studies had measured changes in dynamic compliance after treatment [86,172,221,222,224,225]. The infants showed rapid improvements in oxygenation but no concurrent improvements in dynamic compliance during ventilation.

The improvements in oxygenation have been attributed to documented changes in functional residual capacity (FRC) [158,172,224,236,237]. These observations and conclusions may partly reflect the limitations inherent in measuring dynamic compliance and FRC. Positive end expiratory pressure (PEEP) is usually applied to non-compliant lungs to prevent alveolar collapse at end expiration thereby maintaining FRC. But strictly speaking FRC is the volume of the lungs at end expiration as determined by the balance of the retractile forces of the lungs and the outward recoil of the chest. If the FRC is measured whilst PEEP is being applied then a portion of the volume determined will be attributable to the PEEP rather than to the properties of the lungs and thorax.

If the lung compliance improves, the same PEEP will maintain a higher end expiratory volume than before. This might be sufficient to cause the lung to operate higher up the pressure-volume curve in its flatter portion. Under these circumstances there might be no measurable improvement or even a fall in dynamic compliance but a large improvement in end expiratory lung volume and consequently in oxygenation [34,106,107,235,238]. The single breath technique for measuring static compliance avoids this problem by measuring expired volume from peak inflation to zero (atmospheric) pressure. This has recently been clearly demonstrated by Kelly et al [15] who measured both static and dynamic compliance in a population of infants treated with a naturally derived surfactant and demonstrated significant early improvements in static compliance and oxygenation without improvements in dynamic compliance. The tidal volume did not appreciably change after surfactant treatment but the volume expired to atmospheric pressure increased dramatically indicating that the PEEP was maintaining a higher end expiratory lung volume than before and thereby pushing the lungs up the pressure-volume curve. This improvement in lung compliance at low lung volume was not detectable by the dynamic compliance measurements but was picked up by the single breath technique. The additional volume exhaled to atmospheric pressure on release of the PEEP would have been measurable as an increase in FRC. Gommers et al [204] published a study performed in animals with similar findings of improved compliance at low lung volumes which was less obvious at higher lung volumes. Bartholomew et al [108] recently demonstrated in a population of ventilated newborn infants, many of whom had RDS, that a given change in PEEP had twice the effect on tidal volume as the same change in peak inspiratory pressure, again indicating better compliance at low lung volumes. That is not to say that true FRC does not increase after surfactant treatment. It would have to increase to allow an appreciable increase in compliance because compliance is proportional to the number of alveoli that are inflated. Overdistension of already recruited airspaces would probably reduce compliance.

If the lungs were operating on the flatter portion of the pressure-volume curve because of excessive peak inflation pressure this would lead to underestimation of changes in both dynamic and static compliance. Indeed Kelly et al [15] reported improvements in both static and dynamic compliance when peak inflation pressure was reduced after surfactant treatment. Davis et al [86] found early improvements in dynamic compliance after a administration of a naturally derived surfactant when measurements were made on the infants' spontaneous breaths but not on mechanical ventilator breaths perhaps because there was less overdistension. The infants in our study were unlikely to have been ventilated with excessive peak inflation pressures as their expired volume extrapolated to zero flow and atmospheric pressure was usually 5-10ml/kg or less. Although the static Crs of these infants improved after surfactant treatment and oxygen requirements often decreased substantially the infants still required to be ventilated, often vigorously, and their respiratory compliance did not reach the levels seen in infants without lung disease. Surfactant therefore alleviated but did not cure their respiratory distress syndrome [15].

The observation that in 15/73 (21%) of the infants static Crs before surfactant treatment was consistent with biochemically mature lungs and that in 13/15 of them static Crs fell after treatment raises important questions. Should they have received surfactant? Did it do them more harm than good? The results of the OSIRIS Collaborative Group [202] suggested that early treatment of infants at risk of RDS resulted in a lower overall morbidity than later selective rescue treatment of infants with established RDS despite the treatment of a significant proportion of infants who would not have developed RDS. This would tend to encourage less discriminate use of surfactant to maximise any potential benefits. It remains possible that methods capable at an early stage of selecting out infants unlikely to benefit from surfactant treatment would further improve overall outcome [239]. Furthermore, if as many as 21% of infants could be selected out this would result in a considerable cost saving.

Enthusiasm for such an effective treatment may lead to the ventilation and treatment of more infants than would be necessary [54]. There is evidence that the constituents of naturally derived and synthetic surfactants may be capable of damaging the cell membranes of type II pneumatocytes resulting in cell lysis [240]. Surfactant treatment is associated with an increased risk of pulmonary haemorrhage. Recent work in which disease severity was measured by the CRIB score [241] suggests that surfactant treatment may be associated with increased mortality when given to infants with the mildest disease (Tarnow-Mordi, personal communication). These 15 infants in our study may have had other respiratory problems than RDS which can be difficult to discriminate on an early chest radiograph. If so, the apparently poorer lung mechanics and gas exchange of the 8 "mature" infants after Exosurf may have reflected the adverse effects of the greater volume of fluid instilled into their lungs. The 7 "mature" infants treated with Curosurf still showed a reduction in their oxygen requirements which might reflect more rapid clearance of the smaller volume of administered fluid and continuing improvement in their underlying condition. Animal evidence has suggested that increasing the surfactant dose volume may adversely affect outcome once it is higher than 16% of FRC [242]. Five ml/kg is approximately 25% of a normal human FRC. Whilst our results seem logical in that significant quantitative or functional surfactant deficiency would be unlikely in the absence of stiff lungs, the numbers of observations are small and further studies comparing clinical outcomes would be necessary before it could be recommended that surfactant be given or withheld on the basis of a single lung function test.

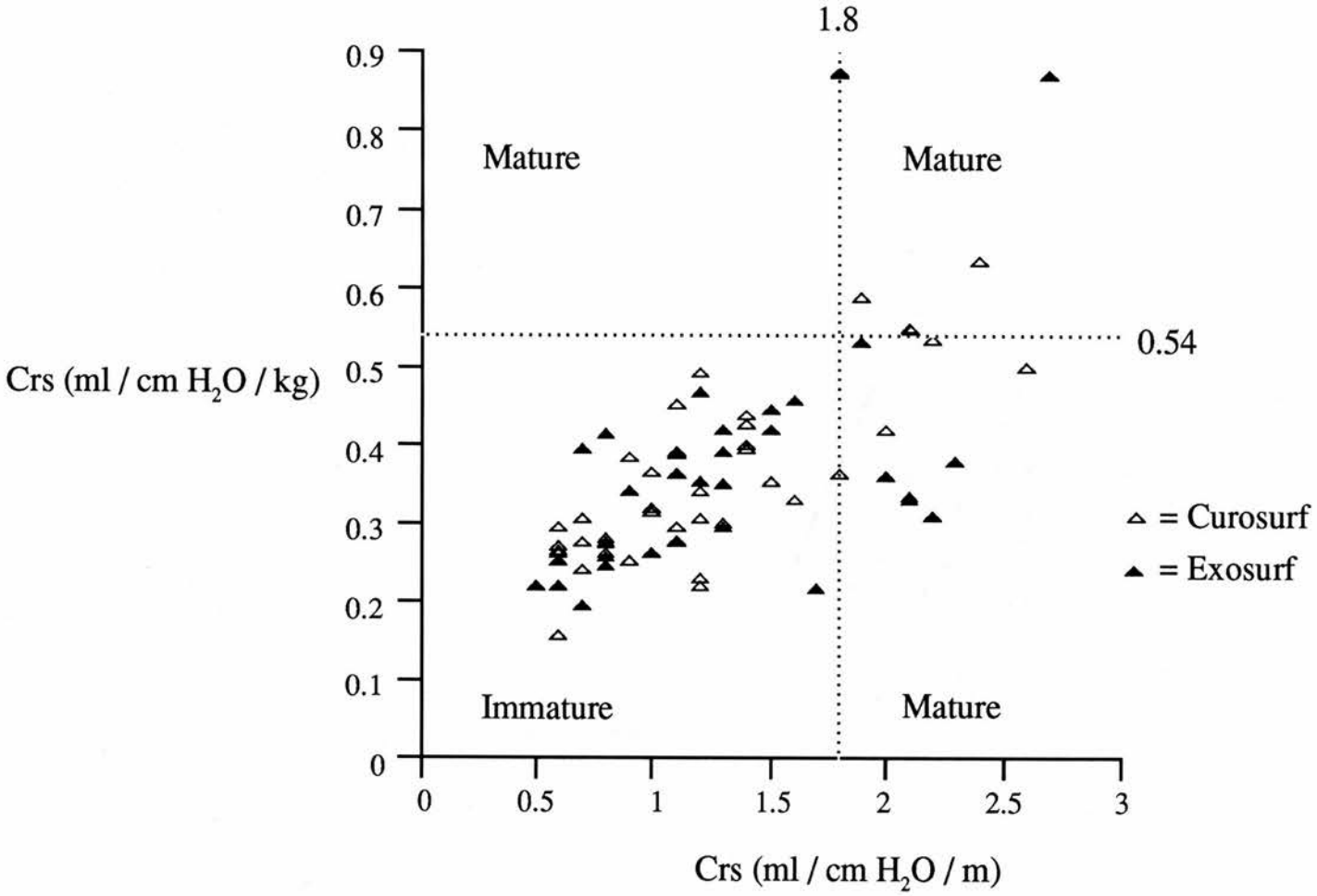
On the basis of two previous studies [59,63] using the same apparatus which suggested that correction of Crs to body length gave more useful information than correction to body weight we corrected our Crs measurements to length. The lack of improvement in Crs after surfactant treatment in 13/15 infants classified as mature (static Crs < 1.8ml/cmH_2O/m) seems consistent with the behaviour of mature lungs.

Had we instead corrected the measurements for body weight using a predefined cut-off for lung maturity of Crs ≥ 0.54 ml/cmH_2O/kg as in a previous study [63], only 5 infants would have been identified as having mature lungs rather than 15 (figure 5.3). Furthermore, 6 of the 8 infants treated with Exosurf whose lung mechanics and oxygenation did not improve would have been identified as immature, which seems inconsistent with their lack of response to surfactant. This finding further supports the suggestion that correction of static Crs for weight in this age group may give less useful information than correction for length.

The rapidity of action of a surfactant may not confer additional benefits. In the Curosurf IV trial [201], infants receiving an initial dose of 200mg/kg body weight of surfactant showed faster improvements in oxygenation and ventilation requirements than those receiving 100mg/kg but there was no significant difference in clinical outcome between the two groups. Minimal handling and avoidance of stress is part of the basic approach to the care of these fragile infants. It could be argued that a surfactant that produced very rapid changes in oxygenation and lung mechanics may place the infant under more stress than one which worked gradually.

In the final analysis the rapidity of action, effect on the lung mechanics or stress of administration of a replacement surfactant are of secondary importance in comparison to the effects on important clinical outcomes such as death, pneumothorax, bronchopulmonary dysplasia, intraventricular haemorrhage and long term neurological deficit. There are no good data to suggest that any preparation is superior to the others in this respect at present. A recent study randomising 600 infants to Exosurf or Survanta [234] showed no statistically significant difference between the two. The power of the study was calculated to be sufficient to detect an absolute difference in the combined incidence of death and bronchopulmonary dysplasia of 11.5% between the two study groups.

Figure 5.3: Crs corrected to weight (kg) in relation to Crs corrected to length (m).



A difference of this magnitude would be extremely important at a national or international level. The 95% confidence intervals for the risk ratios of adverse outcomes between the two surfactants in the study were very close to showing a significant difference and suggested the possibility of a statistical error. The high cost of treatment, the widely different formulations and the differences in acute response to treatment justify much larger studies to determine which surfactant(s) are most effective.

Rapid or slow instillation of Exosurf

Introduction

During the period of these studies evidence from animal models of RDS began to be presented at international meetings that suggested that the mode of surfactant instillation could affect the eventual distribution of the preparation in the lungs and the clinical response to treatment. Ueda et al found that bolus instillation of Survanta (bovine surfactant) into ventilated preterm lambs resulted in a relatively uniform distribution whereas instillation as an infusion over 30 minutes resulted in a much more uneven pattern with 30% of lung pieces receiving almost no surfactant. Segerer et al showed that when Curosurf was instilled rapidly into the lungs of preterm rabbits it was evenly distributed and the response to treatment was good whereas following a slow infusion the distribution was uneven and the clinical response was poor. Both of these studies have since been published [243,244].We had been giving Exosurf as a 30 minute infusion to avoid problems with bradycardia, hypoxia and surfactant reflux that were being experienced by others. Our experience as described above was that over the 12 hours following treatment there was only a small improvement in oxygenation in most cases.

The manufacturers of Exosurf recommended an instillation time of around four minutes as tolerated by the infant and on the basis of our observations, the manufacturers' recommendations and the data of Segerer and Ueda we switched to a more rapid instillation method to see if this would lead to an improved clinical response. From December 1992 onwards all the infants treated with Exosurf in the Simpson Memorial Maternity Pavilion received it as a rapid infusion over 2-5 minutes as tolerated. Their oxygenation and Crs data are presented here for comparison to the infants that had received their Exosurf as a half hour infusion earlier in the study. No Crs measurements were being made in Ninewells Hospital during this period as the investigator in that centre had departed.

Patients and Methods

The indications for surfactant treatment were unchanged from the earlier time period. Exosurf was administered as a rapid infusion into the endotracheal tube connector with the infant lying supine and the head in the midline. The aim was to administer it over 2-3 minutes but administration was slowed if the infant became hypoxic or bradycardic or if surfactant was refluxing back up the endotracheal tube. Occasionally the procedure took 4 to 5 minutes. A second dose of Exosurf was administered twelve hours later to those infants that remained ventilator dependent with a significant requirement for supplemental oxygen. Oxygenation and Crs were assessed in each infant shortly before and 3 and 12 hours after the first dose of surfactant. Ventilation management policies were unchanged between the 2 time periods. Oxygenation was again expressed as the fractional inspired oxygen (FiO_2) required at the time of study to maintain arterial oxygen tension between 6 and 10.3 kPa as in the earlier period of the study. Crs was measured using the single breath technique applying the same data quality criteria as before. The same statistical methods were used.

Results

Satisfactory data were collected on a further 28 infants treated with Exosurf. Their characteristics are detailed in table 5.4. They were again divided according to their pre-treatment Crs. The 24 infants with initial Crs < 1.8 ml/cmH_2O/m were were not significantly different from the infants in the earlier part of the study in birth weight, gestational age, Crs or FiO_2 before treatment. There were 4 infants with initial Crs before treatment that suggested biochemical lung maturity (Crs ≥ 1.8ml/cmH_2O/m).

Table 5.4: Pre-treatment patient characteristics. Data are median (range).

	Initial Crs <1.8 ml/cmH_2O/m	Initial Crs ≥ 1.8ml/cmH_2O/m	All infants
n	24	4	28
Gestation	30 (25-35)	30 (29-31)	30 (25-35)
Birth weight (g)	1355 (687-2750)	1470 (1340-1793)	1393 (687-2750)
M/F	12/12	3/1	15/13
Initial Crs/m	1.0 (0.5-1.6)	1.9 (1.9-2.2)	1.0 (0.5-2.2)
Initial FiO_2	0.70 (0.45-1.0)	0.6 (0.5-0.7)	0.7 (0.45-1)

The changes in Crs and oxygen requirements seen after treatment are shown in figs 5.4 and 5.5. The 24 infants with initial Crs suggestive of surfactant deficiency (Crs <1.8 ml/cmH_2O/m) showed no significant change in Crs either 3 or 12 hours after treatment (fig 5.4). The median (95% confidence intervals) changes were 0% (-14, +6) at 3 hours and +3% (-11, +40) at 12 hours. The corresponding changes in oxygen requirements were -0.22 (-0.1, -0.35) at 3 hours and -0.3 (-0.24, -0.4) at 12 hours. The changes in oxygenation were greater than when Exosurf was administered slowly (median change -0.11 at 3 hours and -0.13 at 12 hours) and the difference between the two methods was highly significant (p=0.028 at 3 hours, p=0.004 at 12 hours).

All four of the infants that had initial Crs suggesting biochemical lung maturity before treatment (Crs ≥1.8 ml/cmH_2O/m) showed a fall in Crs 3 hours after treatment with improvement by 12 hours but unlike their predecessors that had received their Exosurf over 30 minutes they showed improved oxygenation over the study period (fig 5.5).

Discussion

As was found with infusion over half an hour, administration of Exosurf over 2-5 minutes to infants with a clinical and radiological diagnosis of RDS and a Crs in support of the clinical diagnosis resulted in no significant improvement in Crs over the twelve hours following treatment. There is no evidence from any human in vivo study that the immediate clinical response to Exosurf is attributable to early improvements in the lung mechanics. Recently it has been suggested that Exosurf may exert its acute effects by reducing pulmonary artery pressure [245,246] with the effects on the lung mechanics arriving later. This may involve cellular repackaging of the surfactant lipids as exogenous surfactant is rapidly taken up by the lung tissue after instillation [247,248]. Halliday et al [249] were unable to identify early changes in pulmonary blood flow 4 hours after Curosurf despite large improvements in oxygenation.

There was a significant improvement in oxygenation in this group of infants and this was substantially larger than that seen with slow infusion. The infants with initial Crs suggesting mature lungs showed a fall in Crs after treatment as had been noted with slow surfactant infusion.

Figure 5.4: Percentage change in Crs and change in FiO_2 after rapid infusion of Exosurf to infants with Crs <1.8 ml/cmH_2O/m. Data are medians with 95% confidence intervals.

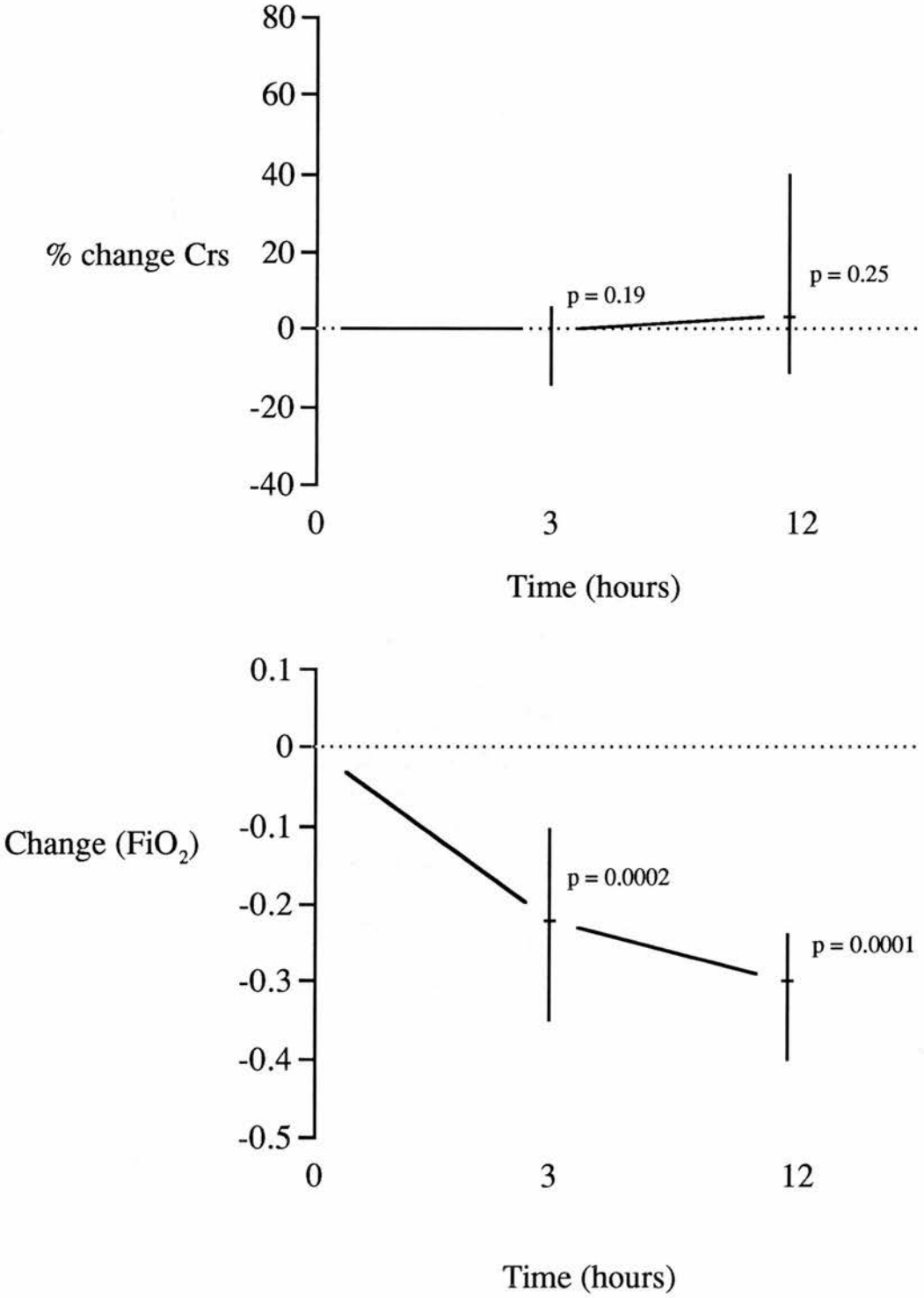
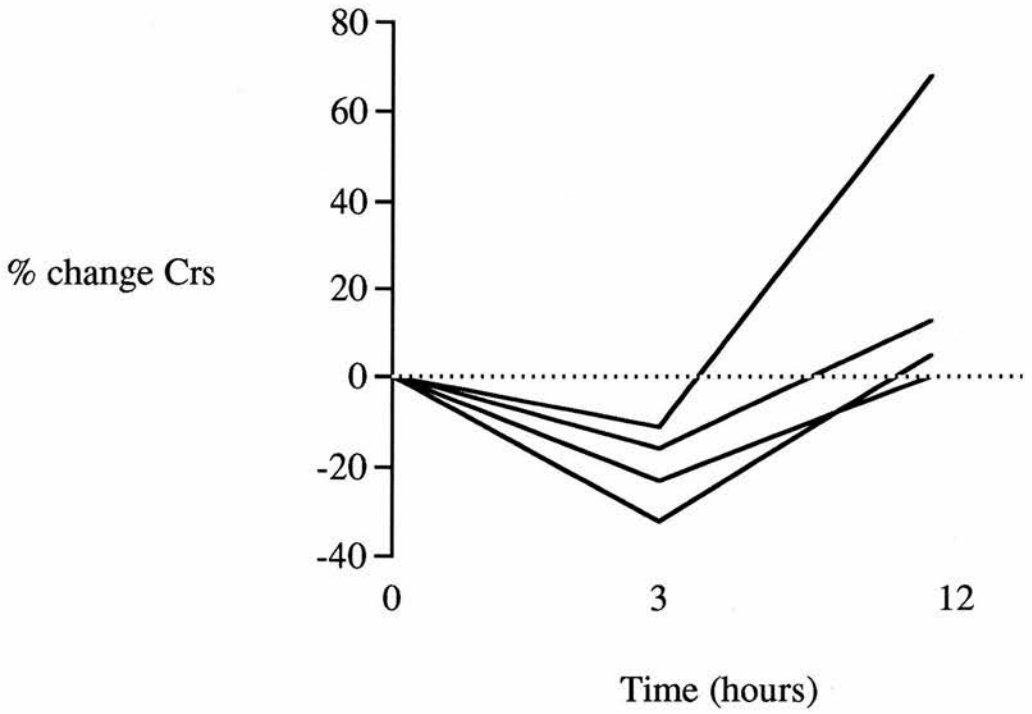
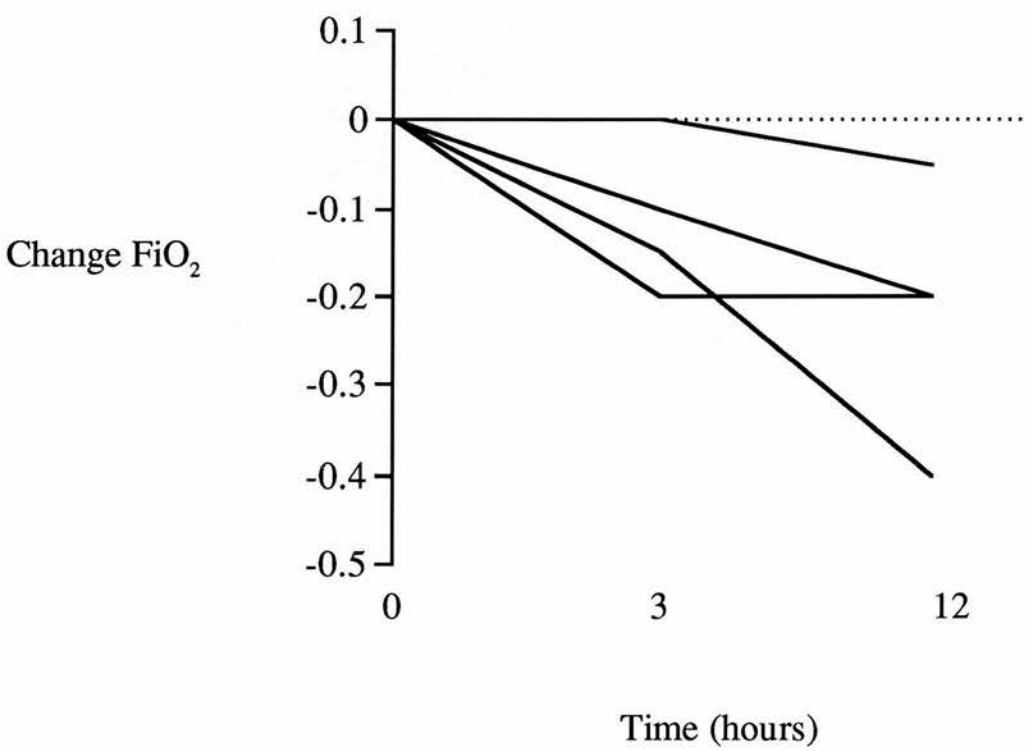


Fig 5.5: Percentage change in Crs and change in FiO_2 after administration of a rapid infusion of Exosurf to infants with Crs ≥ 1.8 ml/cmH_2O/m. Lines represent individual infants.





Although their Crs fell their oxygenation improved during the study period, suggesting either that they had benefitted from their surfactant or at least that unlike their predecessors who received their surfactant slowly they had not apparently been harmed by it.

The difference in surfactant response observed with the two administration methods provides indirect support for the finding from animal models that the method of surfactant instillation has important effects on the distribution of the surfactant within the lungs [243,244]. The findings need not necessarily be confined to Exosurf. The animal studies that raised the issue used Curosurf and Survanta. The treatment allocation in these infants was not randomised and this study supports the hypothesis that surfactant distribution in humans follows the patterns that are seen in animal models but does not prove it. This may be an important area for further prospective study. There is no consensus as to how surfactant should be administered. Many give it rapidly, sometimes manually ventilating the infant for a short period. Others give it as a slow infusion. It may be that the advantages of improved surfactant distribution gained by rapid instillation are outweighed by the harm of the additional stress of the procedure. When Exosurf is given rapidly, oxygen desaturation during administration is seen in up to 40% of infants and bradycardia is also frequently observed [234]. It is increasingly recognised that surfactant instillation is stressful to the infant. This is true of natural surfactant as well as artificial surfactant. Saliba et al [250] found surges in cerebral blood flow velocity and rises in carbon dioxide tension after rapid administration of Exosurf that were not seen following slow infusion over 15 minutes. Cowan et al [251] showed large fluctuations in cerebral blood flow velocity after rapid instillation of Curosurf. Studies performed in Edinburgh have demonstrated large swings in blood pressure and carbon dioxide tension during both natural and artificial surfactant administration [252]. Acute changes in blood pressure have been implicated in the pathogenesis of intraventricular haemorrhage.

Despite its undoubted efficacy in reducing the mortality of respiratory distress syndrome, surfactant treatment has failed to impact consistently upon the frequency of intraventricular haemorrhage. Given that there is diversity of clinical practice around this issue and there are scientific reasons to suppose that either a slow adminstration or a rapid administration policy may be preferable, consideration should be given to randomised controlled trials to determine the optimum policy of surfactant administration.

Chapter 6: Case Histories

Introduction

Although there is still considerable adverse outcome associated with mechanical ventilation very many infants are relatively straightforward to manage and do not develop serious problems. This may mean that for of any study to detect improved clinical outcome resulting from an intervention a very large population sample will be required to avoid a statistical error and that potentially large individual patient benefits may be obscured if smaller samples are studied. When the randomised controlled trial of compliance measurements was planned it was calculated that a sample size of 208 infants would have > 80% power to detect a fall in the incidence of combined adverse outcomes from 40% to 20%. The eventual outcome was that there was no difference between the two groups in the number of infants with one or more adverse events. Despite this, respiratory function data often appeared to make a dramatic difference to patient management resulting in changes of ventilation strategy that were associated with marked clinical improvements. Some of these cases are described.

Inadvertent positive end expiratory pressure

During mechanical ventilation, when lung inflation occurs before the preceding deflation is complete, gas is trapped in the lungs [32]. This gas trapping raises the lung volume and exerts a positive pressure within the airspaces which is not apparent clinically. The phenomenon is called inadvertent positive end expiratory pressure (inadvertent PEEP) [30,31].

Respiratory dead space increases, impairing gas exchange and tidal volume decreases because the effective difference between inspiratory and expiratory pressures is reduced [28,49,106]. Cardiac output may be impaired by the increase in intrathoracic pressure [25,26,29]. The result of unnecessarily high ventilator pressures may be increased adverse clinical outcome such as air leak syndromes, bronchopulmonary dysplasia or even death [35,36].

As described in chapter 1, passive expiratory flow occurs exponentially and the time required for expiration is determined by the expiratory time constant [124,125]. This is the mathematical product of the compliance and resistance of the respiratory system. According to the equation:

$$V = Voe^{-(1/RC)t} \quad \text{.....(Chapter 1)}$$

During passive expiration, after a time (t) equal to 1 time constant (RC), the volume V of gas remaining in the respiratory system of the total inspiratory volume Vo is:

$$V = Voe^{-1} \quad \text{or} \quad \frac{V}{Vo} = e^{-1} = 37\% \text{ (approx)}$$

After one time constant, expiration is 63% complete. After five time constants expiration is 99% complete. After three time constants expiration is 95% complete and clinically important gas trapping is unlikely [13,32]. Increases in compliance or resistance will lengthen the time constant and therefore prolong the time required for efficient expiration. Long expiration times are especially likely to be required where compliance is not severely impaired but airway resistance is high as may be the case in bronchopulmonary dysplasia.

Inadvertent PEEP is frequently observed in ventilated infants [30,104,253]. It can be measured directly in paralysed or hypocapnic patients by occluding the airway exactly at end expiration and measuring the tracheal pressure after sufficient time has elapsed for equilibration [29,30]. This is technically difficult and not practicable in the clinical setting. Alternatively, the presence of inadvertent PEEP can be inferred if the expiration time set on the ventilator is less than 3 time constants. These observations are valid when the respiratory system is behaving as a single compartment with a single time constant. When there is lung disease this may not be the case. Under these circumstances inadvertent PEEP may be inferred if the expiration time set on the ventilator is less than the time spent in expiration when ventilation is interrupted. One study measuring inadvertent PEEP directly [30] found that it was present to at least some degree on 19 of 29 occasions when it was looked for in 10 ventilated infants. There was a small improvement in gas exchange when the ventilation was adjusted to provide a longer expiration time despite lower mean airway pressure being used but inadvertent PEEP did not appear to be making the infants critically ill. Despite the theoretical dangers of inadvertent PEEP there are no reports of infants being seriously harmed by it. In contrast, when adults with chronic obstructive airways disease were ventilated in such a way that resulted in inadvertent PEEP, they often became critically ill [29]. Inadvertent PEEP can be difficult to diagnose clinically. In the following infants it was life threatening. Lung function testing led to its recognition and a change of ventilation led to a dramatic clinical improvement.

Case 1

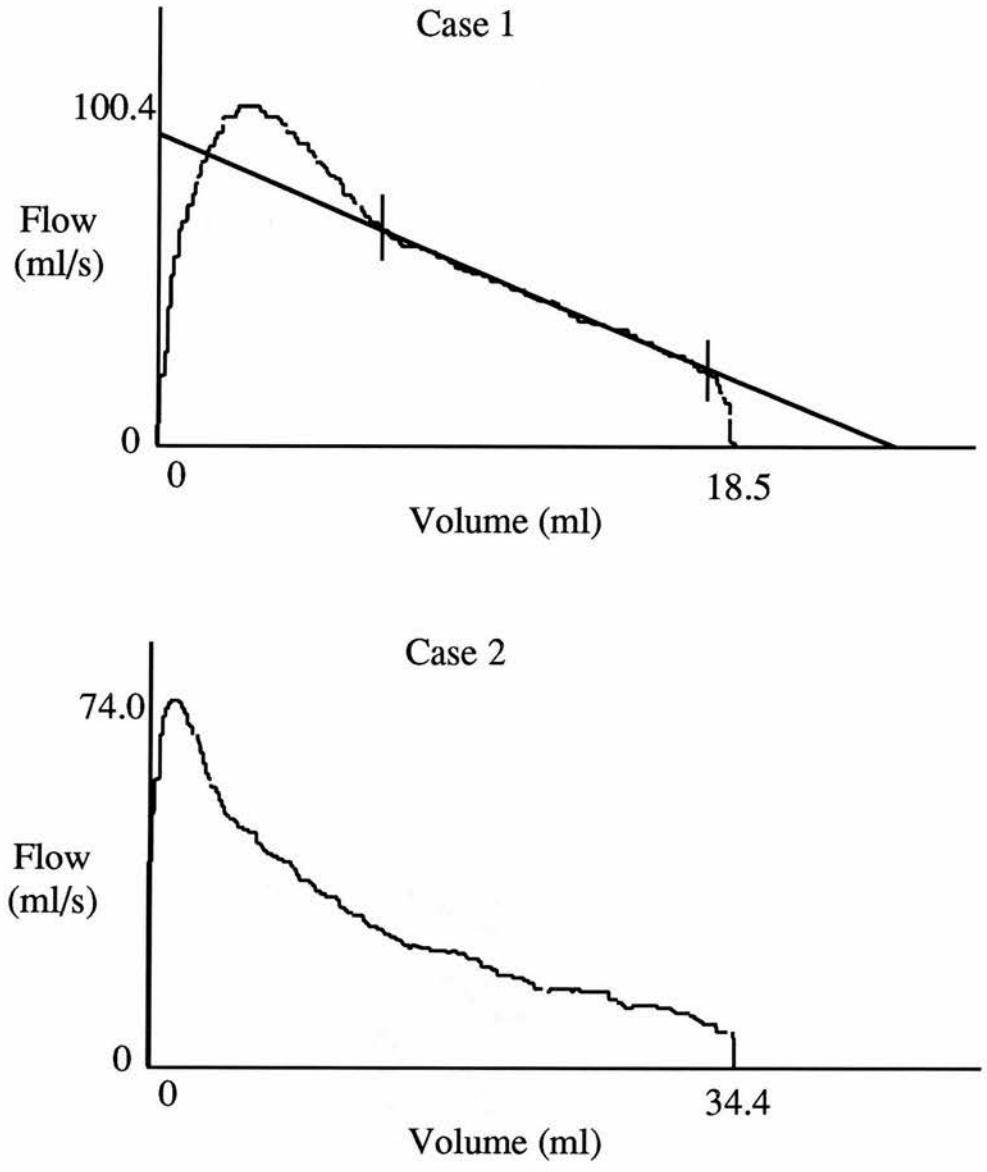
A male infant was delivered vaginally at 25 weeks gestation with birth-weight 890g. He required assisted ventilation initially but did not develop respiratory distress syndrome (RDS) and was extubated on day 4. He collapsed on day 7 and was ventilated and treated with antibiotics for presumed infection, and indomethacin for a patent ductus arteriosus. Following this he remained ventilator dependent.

On day 26 he was on a ventilator rate of 30 breaths per minute (BPM). A chest radiograph showed bilateral hazy opacification and he was given a further course of antibiotics. His condition worsened and by day 32, because of respiratory acidosis his ventilator settings had increased to 50 BPM, with FiO_2 60%. The arterial blood gas tensions showed pH 7.23, pCO_2 6.94 kPa and he was started on dexamethasone. Over the next 3 days he deteriorated. His oxygen requirements increased to 90% and the ventilator rate increased to 60 BPM with pressures 24/5 cmH_2O and inspiration time 0.45 seconds (s). The infant was critically ill and frequently hypoxic. He was reintubated without improvement. The static compliance (Crs), resistance (Rrs) and time constant (τ) of the respiratory system were measured using the single breath technique as described earlier. Figure 6.1 shows the expiratory flow-volume curve. Crs was 3.2 $ml/cmH_2O/m$ (1.0 $ml/cmH_2O/kg$) indicating only mild lung stiffness. τ was 0.26 s giving a time for 95% exhalation of 0.78 s (3τ). The ventilator settings allowed 0.55 s expiratory time. The expired volume to atmosphere was 18.5 ml/kg body weight (normal is 7-9 ml/kg [139]). This indicated severe gas trapping and inadvertent PEEP within the lungs. The ventilator rate was reduced to 40 BPM and the pressures to 16/4 cmH_2O with the inspiration time left constant at 0.45 seconds. The infant's oxygen requirements fell immediately to 50% with no increase in arterial pCO_2 and over the next 18 hours continued to fall to 25%. He was successfully extubated into head-box oxygen 3 days later and discharged home breathing air on day 151.

Case 2

A male infant with birth-weight 1089g was delivered by Caesarean section at 27 weeks gestation because of maternal antepartum haemorrhage. He required assisted ventilation from birth and developed moderate RDS receiving 3 doses of Curosurf (porcine surfactant). He was extubated to nasal CPAP on day 10. From days 12-16 he was re-ventilated with a suspected infection and then extubated.

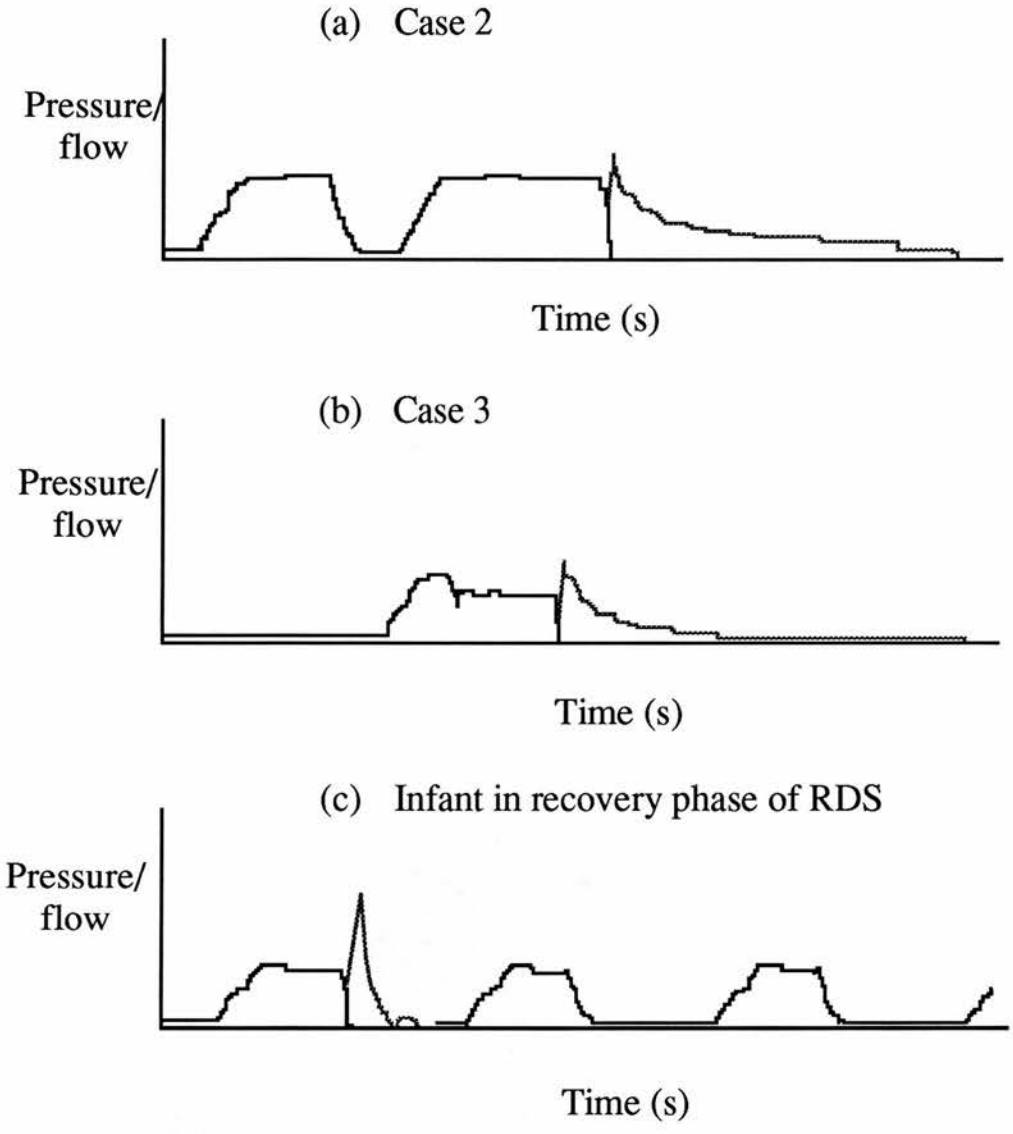
Figure 6.1: Passive expiratory flow-volume curves.



The slope of the straight line extrapolated to the axes in case 1 is equal to the time constant of the respiratory system.

He remained stable in supplemental oxygen until day 30 when his condition deteriorated markedly with recurrent episodes of apnoea and bradycardia and increasing oxygen requirements. The chest radiograph showed generalised patchy consolidation. He was ventilated and his condition stabilised with ventilator settings of 20 BPM, pressures 22/4 cmH_2O, 30% O_2. The following day he became increasingly difficult to ventilate. There were frequent serious desaturations that could only be overcome by vigorous manual ventilation and it was difficult to achieve chest inflation without occluding the pressure relief valve of the bag. A variety of ventilator approaches were attempted utilising both fast and slow rates and none were able to prevent him deteriorating and requiring manual ventilation. His arterial blood gas tensions showed pH 6.9, pCO_2 18.4 kPa, pO_2 7.9 kPa, base excess -8.2. He was reintubated to exclude blockage of the endotracheal tube without improvement. Later that day it was only possible to maintain his gas exchange by manual ventilation with 100% O_2 and he was continuously ventilated by hand for over an hour. Measurement of his lung function was attempted. Because his flow-volume trace was very irregular (fig. 6.1), Crs, Rrs and τ could not be calculated but his expiratory flow-time tracing (fig 6.2) showed that he required an extremely long expiration time (>1.5 seconds) and when complete expiration occurred the expired volume was 23 ml/kg indicating marked over-inflation. The continuous traces of respiratory rate and transcutaneous pCO_2 displayed on his cot-side monitor suggested that higher respiratory rates were associated with higher pCO_2. The infant was paralysed with pancuronium and the ventilator set at a rate of 20 BPM, pressures 25/4, inspiration time 0.6 seconds. The clinical condition stabilised, $PaCO_2$ fell to 3.12 kPa, and FiO_2 settled at 50%. It was now easy to see the prolonged expiratory phase and there was obvious wheeze audible on auscultation that had not been detectable earlier. The presumed cause of this deterioration was infection but aetiology was not proven. He remained dependent on low rate ventilation with low FiO_2 and was successfully extubated on day 53. He was discharged home on day 148 requiring O_2 via nasal cannulae.

Figure 6.2: Airway pressure and expiratory flow v's time. Cases 2 and 3, with tracing from an infant recovering from RDS for comparison (same time scale).



——— Proximal airway pressure during ventilation. Recording stops when ventilation is interrupted to sample passive expiratory flow.

——— Passive expiratory flow from peak inflation to atmospheric pressure.

Case 3

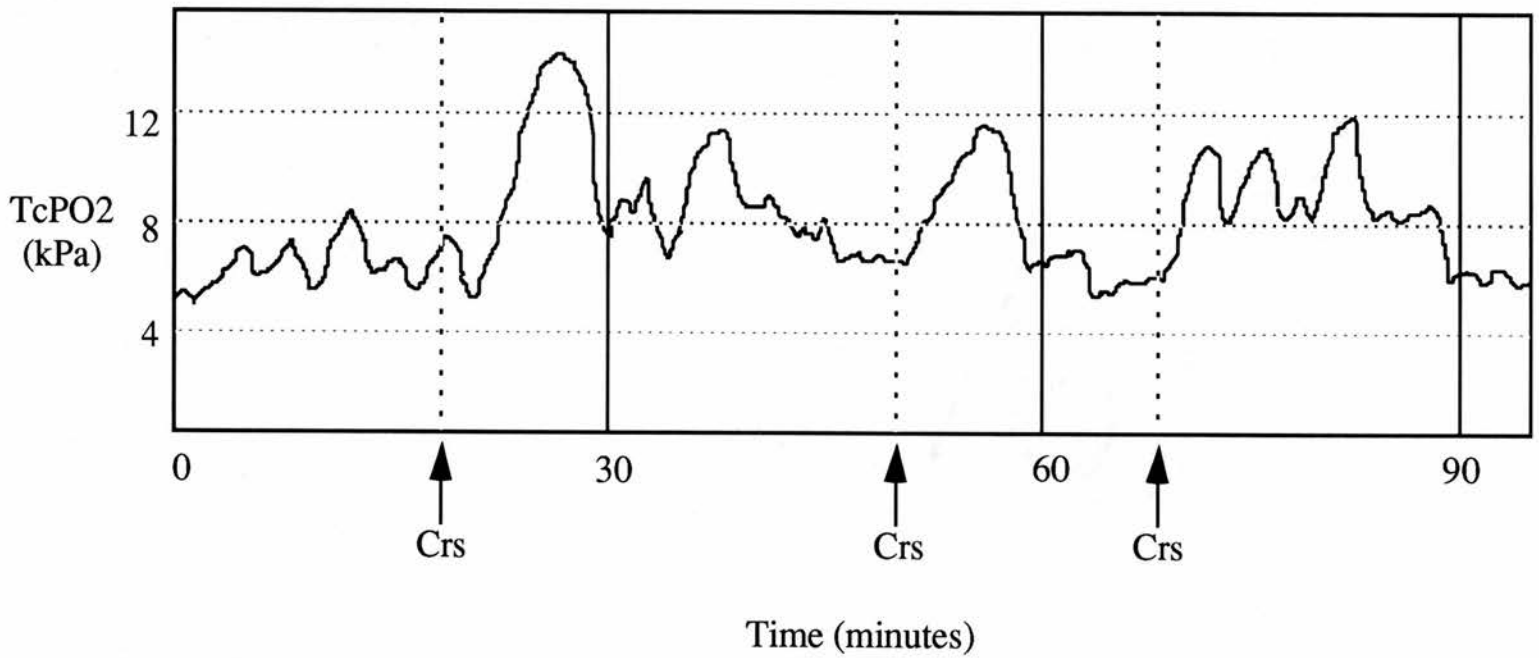
A male infant was delivered vaginally at 27 weeks gestation with birth weight 750g. He was intubated for resuscitation but had no initial lung disease and was extubated into air on day 1. On day 5 his respiratory function deteriorated and he was re-ventilated. Chest radiograph showed slightly increased lung markings and hazy opacification bilaterally. He was treated with antibiotics and was easy to ventilate on low rate, pressures and FiO_2. Over the next few days he continued to deteriorate and by day 10 his chest radiograph showed a bilateral honeycomb appearance. His oxygen requirements had increased to 50% and his ventilator settings were 25 BPM, pressures 22/4 cmH_2O. The oxygen and ventilation requirements continued to increase and on day 14 dexamethasone was started. There was no significant improvement seen and from days 14 to 19 he required > 90% oxygen almost continuously. By this time his ventilator settings had increased gradually to 55 BPM, pressures 24/4 cmH_2O, inspiration time 0.5 seconds, 100% O_2. Re-intubation had excluded endotracheal tube blockage as an explanation for his deterioration. Blood gas analysis showed pO_2 7.3, pH 7.39, pCO_2 5.04. There was no clinical improvement with nebulised ipratropium bromide. Because of his respiratory efforts, measurement of lung function was impossible until he was paralysed with pancuronium. It was then demonstrated that the expiration time was markedly prolonged (fig 6.2). The volume expired to atmospheric pressure was 17.5 ml/kg indicating that gas trapping would be expected with the ventilator settings prior to paralysis. The infant was ventilated at a rate of 25 BPM with pressures 24/4 cmH_2O, inspiration time 0.6 seconds and expiration time 1.8 seconds. His oxygen requirements fell rapidly and were 30% five hours later with a minimal increase in pCO_2. Pancuronium was discontinued after 3 days and the infant was extubated on day 37. He had continuing problems with bronchopulmonary dysplasia until discharge home on day 275 at which time he had been breathing air for one month.

Case 4

A male infant weighing 737g was delivered at 26 weeks gestation by emergency Caesarean section for maternal pregnancy induced hypertension. He required ventilation from birth and developed RDS receiving 3 doses of Curosurf. His respiratory function improved but he remained ventilator dependent on low rate, pressures and FiO_2. On day 9 he became pyrexial and was handling less well. His ventilation and oxygen requirements were increasing. A blood culture grew coagulase negative staphylococci. Chest radiograph showed bilateral patchy opacification. The infant was treated with vancomycin. The ventilation requirements carried on increasing and by day 17 he was on pressures 22/4 cmH_2O, rate 60 BPM, inspiration time 0.4 s and in 90% O_2. Repeat chest radiograph showed a bilateral honeycomb pattern. Lung function testing showed that the lungs were not stiff. Crs was 2.5 ml/cmH_2O/m (1.0 ml/cm H_2O/kg). The time constant was 0.3 s suggesting that inadvertent PEEP may be a problem on the ventilator settings being used. The infant was in the study group whose Crs could not be revealed. Five hours later the infant was in 98% 0_2 on the same ventilator settings. Arterial blood gases showed pH 7.16, $PaCO_2$ 9.22 kPa, PaO_2 7.6 kPa. The pressures were increased to 25/4 cmH_2O without improvement. Pancuronium was given with no significant immediate change in condition and 3 hours later the FiO_2 was still 90%. The $PaCO_2$ had fallen to 4.39 so the ventilator rate was reduced to 50 and then 40 BPM. The FiO_2 fell to 75% and then 40% with the successive reductions in rate and $PaCO_2$ fell to 3.69 kPa. The infant had a long and difficult course from this point onward including the development and treatment of necrotising enterocolitis (NEC). He was still ventilated on day 44 when his 2 weeks of antibiotics and parenteral nutrition for NEC were completed. He co-ordinated poorly with the ventilator and it was proving difficult to wean him off it so he was started on dexamethasone. Shortly after this he was extubated onto nasal CPAP but this failed to stabilise him and he was reintubated and ventilated at a low rate.

Because of poor co-ordination with the ventilator he was placed on patient triggered ventilation (PTV) on day 55 using an SLE 2000 ventilator in assist-control mode with pressures 20/4 cmH_2O and inspiration time 0.44 s. His FiO_2 during the 12 hours prior to commencing PTV was mostly 24-40%. The infant triggered at a rate of around 60-65 BPM for the next 2 days and did not appear to be auto-cycling. Soon after the commencement of PTV the FiO_2 rose to 65% and remained steady around this value. Lung function measured during this time showed Crs 3.4 $ml/cmH_2O/m$ (0.9 $ml/cmH_2O/kg$) indicating that the lungs were not stiff. The time constant was 0.24 s. This suggested that the infant required 0.72 s to efficiently exhale. The average expiration time allowed by the ventilator at a trigger rate of 65 BPM was 0.52 s. The expired volume to atmospheric pressure was 16.2 ml/kg. The lung function measurements were made at three time points over the space of an hour. On each occasion that the measurements were made the transcutaneous pO_2 increased dramatically as ventilation was interrupted and the trapped gas was released (fig 6.3). These findings suggested that the infant was self-administering inadvertent PEEP through the trigger ventilator and that this had caused the oxygen requirements to increase. The blood gases at this time showed pH 7.38, $PaCO_2$ 6.06, PaO_2 6.6. The following day the infant self-extubated from the same settings and never required re-ventilation. He was discharged home on day 167 breathing air, with low flow O_2 available should it be required.

Figure 6.3: Transcutaneous PO_2 ($TcPO_2$) trend data. Case 4.



Discussion

The airway obstruction common in bronchopulmonary dysplasia makes inadvertent PEEP especially likely to occur. Perhaps it should have been anticipated in these cases. However their problems evolved gradually and the ventilator rates had been slowly increased in response to respiratory acidosis which developed at lower rates. The infants were examined frequently by experienced clinicians. Chest hyperinflation was not apparent clinically or radiologically. Chest movement with the ventilator gave the impression that the lungs were stiff and expiration did not appear prolonged. Gas trapping can force tidal volume exchange to occur further up the lung pressure-volume curve in its flatter portion where compliance is reduced and resistance may also be lower [32]. This would tend to make the early part of expiration more rapid. Under these circumstances expiration during the time allowed by the ventilator settings may not appear prolonged and this may only become apparent if ventilation is interrupted. The infant's own respiratory efforts may also confuse the issue. In case 2, low rates were tried without improvement and it was only when they were imposed by the addition of pancuronium that success was achieved. It is tempting to assume that the problems were simply due to the infant's reluctance to co-operate with the ventilator. However, in case 4 the oxygen requirements did not fall after paralysis but fell dramatically after the ventilator rate was reduced and later inadvertent peep was observed when the infant was apparently comfortable and breathing quietly on PTV.

Our experiences suggest that unrecognised inadvertent PEEP may be a widespread and serious problem. Although the techniques exist, we did not measure the actual amount of inadvertent PEEP directly as this would be technically difficult in such sick infants on such rapid respiratory rates. The actual level is not particularly important once it is recognised that it is causing impaired gas exchange as the time constant, expiration time or expired volume to atmospheric pressure will give sufficient information to allow the ventilator to be adjusted appropriately.

Diagnosis of RDS

Surfactant replacement is established as a proven, effective treatment for RDS on the basis of a large number of well designed randomised controlled trials. There are however a significant number of infants who either show a poor response to surfactant or whose condition is apparently worsened following surfactant administration. Various explanations have been put forward for this phenomenon [254,225]. Now that there is such an effective treatment for RDS it is to be expected that the diagnosis may be made more frequently than before [54]. Under these circumstances more infants who are not surfactant deficient may receive treatment.

Case 5

A female infant was delivered vaginally at 34 weeks gestation with birth weight 1980g. Her mother had had ruptured membranes and chronic liquor leakage with consequent oligohydramnios since 20 weeks gestation. She had received many courses of dexamethasone prior to delivery. The infant was in good condition and was not considered to need resuscitation before transfer to the neonatal unit. She was noted to have marked bilateral talipes equinovarus, flexion contractures of the elbows and knees and squashed looking facies. On arrival in the neonatal unit she was cyanosed and was given facial O_2. She required intubation and ventilation and it was difficult to inflate her lungs without occluding the pressure relief valve on the resuscitation bag. To achieve adequate ventilation she required ventilator pressures of 40/5 cmH_2O, inspiration time 0.8 s and her ventilator rate was set at 35 BPM. Chest radiograph suggested small poorly inflated lungs and the clinical impression was one of pulmonary hypoplasia. It was possible to reduce her pressures after a few hours to 32/6 cmH_2O maintaining the inspiration time at 0.8 s. A repeat chest radiograph showed some interstitial emphysema and the chest appeared a little bell shaped.

After 6 hours of ventilation the FiO_2 was still 60% and the chest inflation still appeared poor so in view of the infant's prematurity it was decided to give her surfactant. Her ventilator settings at this point were 32/6 cmH_2O, inspiration time 0.8 s, rate 35 BPM. Her lung function was measured and it was immediately obvious that although the chest movements with the ventilator were poor, when ventilation was interrupted and the infant allowed to exhale to atmospheric pressure the chest movement was large. The exhaled volume to atmospheric pressure was 15 ml/kg and the flow-volume curve appeared very overdistended. The ventilator pressures were reduced until the exhaled volume was in the range 5-10 ml/kg and satisfactory flow-volume curves for compliance measurements were obtained. The compliance was 2.3 $ml/cmH_2O/m$ (0.5 $ml/cmH_2O/kg$) indicating that although the compliance was reduced it was not markedly so. The ventilator settings were pressures 17/3 cmH_2O, inspiration time 0.5 s, rate 40 BPM. The infants O_2 requirements rapidly fell to 30% and there was no increase in $PaCO_2$. Surfactant was no longer considered to be clinically indicated. The infant was extubated on day 3. The initial impression of pulmonary hypoplasia was revised to dry lung syndrome [255,256].

Case 6

A male infant was delivered at 31 weeks gestation by Caesarean section for maternal pregnancy induced hypertension with birth weight 1245g. He was ventilated from birth and a chest radiograph was consistent with RDS. At 5 hours of age the ventilator settings were 30 BPM, inspiration time 0.5 s and pressures 23/4 cmH_2O. The FiO_2 had been 60% since birth and the blood gases on these ventilator settings were pH 7.42, PaO_2 5.4 kPa, $PaCO_2$ 4.66 kPa. It was decided to treat the infant with surfactant. Crs before treatment was 2.7 $ml/cmH_2O/m$ (0.86 $ml/cmH_2O/kg$) indicating that the lungs were not stiff. This value is well above the level previously associated with surfactant deficiency [63]. The infant was in the study group whose compliance data were not revealed.

Exosurf was given and the infant's respiratory function steadily deteriorated. Three hours after treatment the Crs had fallen to 1.6 ml/cmH_2O/m (0.53 ml/cmH_2O/kg). The FiO_2 had increased to 90% on the same ventilator settings. Twelve hours after treatment the Crs was 1.3 ml/cmH_2O/m (0.42 ml/cmH_2O/kg), and the infant was requiring 98%O_2. He had been started on pancuronium, the ventilator rate had been increased to 60 BPM and the pressures to 26/4 cmH_2O. A further dose of Exosurf was given. Three hours later the Crs was 0.7 ml/cmH_2O/m (0.22ml/cmH_2O/kg) the FiO_2 was 85% and the ventilator settings unchanged. Twelve hours later the Crs was 0.6 ml/cmH_2O/m (0.2ml/cmH_2O/kg), a value previously associated with a high risk of death [59]. No further surfactant was given. From this point onwards the respiratory function gradually improved and ventilation was able gradually to be weaned. By day 6 the Crs had increased to 1.8 ml/cmH_2O/m (0.58ml/cmH_2O/kg) and the infant was ventilated on low rate and pressures and was breathing air. He was successfully extubated the following day but went on to develop bronchopulmonary dysplasia and was oxygen dependent until his expected date of delivery.

Discussion

These situations arose when the clinical impression was that the lungs were much stiffer than the Crs suggested. This clinical impression was probably influenced by the history in case 5 and the birth weight and gestation in case 6. The infant described in case 5 would reasonably have been felt to have pulmonary hypoplasia and or surfactant deficiency in the absence of lung function measurements, but the clinical course once the ventilator was adjusted was not typical of either. Considered alone and without the lung function data the clinical course seen in case 6 might seem typical of severe RDS. However this infant was one of the 19 infants described in chapter 4 with pre-surfactant Crs suggestive of biochemically mature lungs. Seventeen of these infants showed a fall in Crs after surfactant treatment.

Six of the 8 infants in this group that were treated with a slow infusion of Exosurf showed increased oxygen requirements after treatment whilst the infants with low compliance before Exosurf showed reduced oxygen requirements after treatment. The median Crs measured in the 24 hours before successful extubation of 100 infants in the randomised trial was 2.6 ml/cmH_2O/m. This infant was easily to ventilate before treatment and became critically ill after successive doses of surfactant and his Crs before treatment was 2.7 ml/cmH_2O/m (0.86 ml/cmH_2O/kg). It is most likely that he never had surfactant deficiency and quite possible that surfactant treatment was harmful in his case.

Given the poor agreement between estimates of Crs made by junior doctors and those of their colleagues and between estimates of Crs made by junior doctors and measured Crs that were demonstrated in chapter 2 it is not surprising that there were cases where Crs measurements appeared to be clinically important. These are only individual cases however and it is possible that there were other occasions when the compliance data were rightly ignored as potentially misleading, although these were not obvious. This collection of cases may reflect artificially well on the potential usefulness of compliance measurements. Nevertheless they are persuasive and in combination with the data presented in the preceding chapters are supportive of the basic hypothesis that some form of lung function monitoring may have a place in clinical care.

Chapter 7: Summary and General Discussion.

During the last decade neonatal intensive care has moved a long way forward in its efforts to conquer the respiratory consequences of premature birth. The widespread use of antenatal steroids means that far fewer infants than before develop respiratory distress syndrome. Replacement surfactant dramatically improves the outlook for those who do. Yet despite the improvements in equipment and expertise many infants still die of respiratory disease and we still face the challenge of chronic lung disease. The infants who are developing chronic lung disease are now considerably smaller and less mature than those originally described by Northway [257] but our success in keeping them alive means that this problem is increasing rather than decreasing.[10,21]. The annual cost of caring for infants with chronic lung disease in the United States has been estimated at $2.4 billion [258].

It may be that not all of the increase in chronic lung disease can be attributed to increased survival alone [259]. There is certainly substantial variation between treatment centres in its frequency. Avery et al [260] compared the incidence of CLD between large treatment centres in the United States. One centre had considerably less CLD than the others. The only important difference that was identified in management style between the units was that the successful centre had a policy of a gentler and more permissive approach to mechanical ventilation with early institution of nasal continuous positive airway pressure soon after birth.

A recent retrospective analysis of the risk factors for the development of CLD in a group of infants randomised into a multicentre surfactant study found a five times higher risk of CLD to be associated with a low arterial carbon dioxide tension in early life after controlling for known potential confounders [261]. The interpretation of this finding was that for a ventilated preterm infant with a diagnosis of RDS to have a low carbon dioxide tension in early life, the recruited alveoli must be being over ventilated and placed at higher risk of lung injury. Chronic lung disease is undoubtedly multi-factorial in origin [258,262] but few would contest the central role of mechanical ventilation. If as suggested lung injury caused by ventilation can be decreased by more effective ventilator management this must be seen as a very important goal.

The mechanical ventilation of newborn infants is a constantly evolving process. The basic time cycled, pressure controlled continuous flow ventilators of the 1970's and 1980's are being joined by a new generation of ventilators that offer ever more modes of support. As well as having to pick up the basic principles of respiratory physiology and time cycled pressure controlled ventilation, the newcomer to neonatology may now have to pick up the concepts of patient triggered ventilation (both assist control and synchronised intermittent mandatory ventilation with various methods of triggering), high frequency oscillatory ventilation, high frequency jet ventilation, pressure support and volume controlled ventilation, as well as combinations of these. Some of these newer ventilators are also beginning to incorporate varying degrees of inbuilt respiratory function monitoring. Junior doctors are unlikely to develop real expertise on so wide a front given the shortening of their training. Many of these innovations are evolutions that grew up as imaginative solutions to perceived shortcomings in the existing technology and as such they should be greeted with enthusiasm.

However none of them has yet emerged from rigorous real life evaluation with clear evidence based on clinical outcomes to document their superiority over earlier techniques. Medicine is already crowded with "established treatments": of uncertain worth. There is a responsibility to prevent their number increasing. More and more, "evidence based medicine" is seen as the standard of care of the future [263].

The objective of these studies was to evaluate the potential for regular measurements of the static compliance of the respiratory system using the single breath technique to improve the care and outcomes of mechanically ventilated newborn infants. There are still no published studies demonstrating that any form of lung mechanics monitoring could achieve this aim. There are already commercial systems obtainable for measuring the lung mechanics using either dynamic or static techniques and many small studies providing persuasive evidence that their introduction has the potential to improve clinical care. The single breath technique was selected for these studies because in comparison to dynamic techniques it appeared less complicated with problems of interpretation.

In the present studies the single breath technique was found to be safe in this population of infants with over a thousand episodes of measurement being tolerated without significant complications. No scientific study of the physiological effects of the measurements was performed, but Simbruner et al [264] found no significant effects on heart rate, respiratory rate and oxygenation when they applied a similar technique to a series of 12 newborn infants. Measurements of Crs in ventilated infants should ideally be performed reasonably close to endotracheal suction to avoid any distortion of the results by secretions so if the adoption of this technique required very frequent measurements it would result in more episodes of suction and that might be harmful.

The technique has been described as "readily learned" [63]. The mechanics of operating the apparatus and obtaining data recordings were not difficult but a large body of knowledge has been amassed concerning every aspect of the methodology and its pitfalls which the user needs to be familiar with. This would complicate its more widespread introduction. Because of the problems of active infants, air leaks around the endotracheal tubes, and lungs whose behaviour could not be described by a single compartment model there were many occasions where measurements were not successful. Other authors of studies using the single breath technique in ventilated infants have acknowledged the failure of the technique in some infants but not reported the failure rate. Fletcher et al [138] were unable to record satisfactory Crs data using the single breath technique in 5 of 16 older infants. Their infants were not intubated. This failure rate is a serious disadvantage in comparison with on-line dynamic techniques which will give at least some information all the time. The success rate of individual studies could be improved by sedating or paralysing the infants but if the technique is to be promoted for regular non-invasive monitoring throughout the duration of mechanical ventilation this would not be practicable or desirable.

In chapter 2 it was found that junior doctors estimates of Crs agreed poorly both with one another and with an objective measurement. This should come as no surprise. Other studies considering the clinical skills of doctors have been similarly unimpressive [58]. That they should adopt opposite poles on several occasions was rather worrying. It is a concern of the Medical Educational Bodies that curricula are becoming too heavily fact-laden with a consequent loss of available time for clinical skill acquisition [265]. With the shortening of post-graduate training, clinical skill levels are unlikely to improve.

Clinical decision support systems are likely to develop increasing popularity provided that they stand up to scrutiny. It would have been interesting to examine more rigorously whether the judgements made by consultants were any better than those of their juniors but this was not possible at the time of these studies.

In chapter 3 the principal finding of the randomised controlled trial was that the single breath technique used routinely as an aid to management in 123 ventilated infants had no effect on their outcomes in comparison to 122 control infants. The numbers of adverse outcomes experienced by the two groups were very similar which makes it difficult to entertain the possibility that this finding might represent a type I statistical error. The finding of a significantly reduced duration of ventilation in survivors accompanied by a similar but smaller (non-significant) reduction in the duration of ventilation in the experimental group over the study as a whole suggests the possibility of a type II error over this outcome. A larger multicentre study could be planned to test this hypothesis. Were the hypothesis proven the difference in resource usage between the two groups would certainly have the potential to result in considerable cost savings nation-wide. It is doubtful whether such a study would be attractive to other units. It would require a large investment of energy for a study that would not be expected to improve the major outcomes of neonatology. There are more pressing issues for collaborative study such as the use of nitric oxide, oscillatory ventilation, pain management and corticosteroid treatment. It is possible that the study design was not adequate to evaluate fully the potential of the technology. The results of the measurements and their interpretation were simply written on the blood gas sheets and it was left up to the clinicians to act according to their own judgement. A more prescriptive approach might have worked differently. But if the technique were ever to find its way into routine care it would be as a source of additional information rather than as a prescriptive ventilation management system.

Another potential confounder in the trial is that lessons learned from infants in the experimental group may have been applied successfully to the infants in the control group. Once several infants had been shown to improve greatly when their ventilator settings were adjusted to avoid inadvertent PEEP, the clinicians became much more wary of it and looked for it even in the absence of Crs data that suggested it.

In chapter 4 the reproducibility of the single breath technique was found to be acceptable for clinical use and at least comparable to that of other techniques. This was assessed in the two study investigators who had gained considerable experience in the technique by this time. It remains to be seen whether any of the techniques proposed for respiratory function monitoring in the sick newborn infant are as reliable in the hands of a number of different members of the on-call staff who would by necessity have less experience in their use. Ease of use would be an argument in favour of automated on-line techniques.

In chapter 5 the finding that a value of Crs which predicted biochemical lung immaturity in one study predicted the response to surfactant replacement in another represented a biological validation of the objectivity of the technique. The finding of improved Crs after Curosurf helps to explain the mechanism of action of surfactant treatment in human infants with RDS. It is by no means the sole explanation however. Just as the Exosurf treated infants showed some early clinical improvements a number of infants showed good clinical response to Curosurf without showing improved Crs. Possible explanations for this have already been discussed. The difference in response between natural and artificial surfactant is likely to be important. An increasing number of studies comparing natural and artificial surfactant have been published. Considered alone they do not favour any one surfactant but considered together the case for preferring naturally derived surfactant to artificial surfactant is strengthening [266].

The greater surface activity of natural surfactants appears to be attributable to the presence of the apoproteins SP-B and SP-C. There is now interest in whether or not the addition of the other apoproteins SP-A and SP-D will confer additional benefits [267]. Of 19 infants with initial Crs $\geq$ 1.8 ml/cmH_2O 17 showed a fall in Crs after surfactant treatment. This consistent finding promotes the hypothesis that there may be a group of infants with a clinical diagnosis of RDS that can be identified prospectively as being unlikely to benefit from treatment. They represent around 20% of all infants currently treated. This finding requires prospective study. If pilot work demonstrates that there is no obvious harm associated with non-treatment then a 20% reduction in surfactant usage would be a worthwhile goal. Aside from the large cost savings, surfactant administration is increasingly recognised as a significant stress to the fragile infant at risk from intraventricular haemorrhage. This finding coupled to the observations that clinical assessments of Crs tend to be poor suggests that this is an area where some kind of lung function testing may have a real future. This is not an issue if prophylactic treatment of RDS is the preferred approach but there is no good evidence to suggest that prophylaxis is superior to very early selective rescue treatment. The early changes in Crs after surfactant treatment were often quite large. Certainly they were large enough to warrant alterations to the ventilator settings. It is important to remember that these changes were undetectable using the on-line dynamic techniques that are becoming popular, probably because of dynamic pulmonary hyperinflation attributable to the positive end expiratory pressure being applied [15].

What is the future for the clinical application of lung function testing in the neonatal population? These studies would imply that there is unlikely to be a place outside the research setting for the single breath technique as it currently stands. For research purposes such as the evaluation of new treatments it has so far stood the test of time as well as any other technique.

Newer ventilators provide large amounts of information on tidal volume and minute volumes and on pressure, flow and volume and their relationships with time. The manufacturers are less quick to provide rigorous data on the accuracy of these measurements over the ranges encountered or on their frequency responses and phase relationships. There is a long way to go before it can be teased out just how much of this information is useful and under what circumstances. This is an important research priority as there is presently considerable information overload with these systems. Given the increasing evidence that lung injury is caused by volume overdistension there seems little doubt that measurements of volumes will find some place. Interpretation of dynamic pressure-volume loops can provide useful information but requires skill and experience. They may enable the detection of lung overdistension [111]. There is a need for more data concerning their frequency dependence. Flow-volume loops likewise may be helpful in determining changes in resistance patterns and adequacy of the set expiration time. It is likely that such loop appearances can be described mathematically and screened for by on-line computer so that an appropriate warning message such as "over-inflation, consider reducing inspiratory pressure" or "incomplete expiration, increase expiration time" can be displayed and acted upon without the need for expertise in direct interpretation of the loops. Work needs to be done on the sensitivity and specificity of algorithmic analyses such as this before they can be introduced. The concern remains that these approaches will not detect excessive end-expiratory pressure and that as a result even "normal" tidal volumes may be seriously overinflating the lungs. It may be that more readily applicable techniques for measuring FRC will enable this problem to be overcome. Alternatively an integrated ventilator/monitoring system capable of venting rapidly to atmospheric pressure would allow complete information about expiratory volume to be obtained to complete the picture.

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Appendix Publications arising from these studies

Permission has been obtained from the publishers for the inclusion of the following photocopies.

Static respiratory compliance in the newborn. III: Early changes after exogenous surfactant treatment

Ben J Stenson, Rebecca M Glover, Gareth J Parry, Rosalie A Wilkie, Ian A Laing, William O Tarnow-Mordi

Abstract

Static respiratory system compliance (Crs) was measured by a single breath passive expiratory flow technique in 73 newborn infants treated with exogenous surfactant. The first 39 received Curosurf, a natural porcine surfactant. The other 34 received Exosurf Neonatal, a synthetic surfactant. All had a diagnosis of respiratory distress syndrome with an arterial/alveolar oxygen ratio <0·22. Static Crs and arterial blood gases were measured shortly before, and at three and 12 hours after the first dose of surfactant. In 32 infants treated with Curosurf with initial static Crs <1·8 ml/cm H_2O/m body length, which is consistent with surfactant deficiency, static Crs improved by 18% at three hours and by 39% at 12 hours along with a median reduction in fractional inspired oxygen (FIO_2) at three hours by 0·32. In 26 infants treated with Exosurf with initial Crs <1·8 ml/cm H_2O/m, Crs did not improve three and 12 hours after treatment and oxygenation improved less than after Curosurf, with a median reduction in FIO_2 at three hours of 0·11. Fifteen of the 73 (21%) infants had initial static Crs of ≥1·8 ml/cm H_2O/m, not consistent with surfactant deficiency. Thirteen of these 15 infants showed a fall in static Crs after surfactant treatment, raising the question whether exogenous surfactant did them more harm than good. Initial static Crs and surfactant type both appear to determine the early response to the first dose of surfactant. Only a considerably larger, randomised study can show which surfactant is more effective in reducing adverse clinical outcome.

(*Arch Dis Child* 1994; 70: F19–F24)

Department of Child Life and Health, University of Edinburgh
Ben J Stenson
Ian A Laing

Centre for Research into Human Development, Department of Child Health, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY
Rebecca M Glover
Gareth J Parry
Rosalie A Wilkie
William O Tarnow-Mordi

Correspondence to:
Dr Tarnow-Mordi.

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The early clinical response to exogenous surfactant treatment is variable, but there is usually a rapid improvement in oxygenation and a reduction in requirements for ventilatory support. Concurrent improvements in lung mechanics have been demonstrated in animals[1–4] but most studies in ventilated human infants have not shown consistent early changes in lung mechanics after exogenous surfactant.[5–11] This inconsistency may reflect differences both in methods of measuring lung mechanics in infants and between various surfactants. Changes in dynamic compliance after surfactant treatment are more susceptible to distortion by ventilator management than changes in static compliance measured concurrently in the same infants.[12] Naturally derived surfactants appear to have a more rapid clinical effect than synthetic ones.[4] We report changes in lung mechanics in infants treated with natural and synthetic surfactant, using a single breath passive expiratory flow technique to measure the static compliance of the respiratory system (Crs).

Patients and methods

SURFACTANT TREATMENT

Newborn infants admitted to the teaching hospitals in Dundee and Edinburgh were studied between August 1991 and August 1992 as part of a randomised controlled trial to test the hypothesis that regular information about respiratory mechanics improves clinical outcome in mechanically ventilated neonates.

Infants from both centres were treated with surfactant if between 2 and 72 hours of age they required mechanical ventilation for respiratory distress syndrome and had an arterial/alveolar oxygen (a/A) ratio <0·22. Between August 1991 and December 1991 infants were treated with Curosurf (Chiesi Farmaceutici) according to the protocol of Curosurf 4,[13] a trial of alternative dose regimens. From January 1992 to August 1992 infants received Exosurf Neonatal (Wellcome).

Curosurf is a preparation of polar lipids, isolated from minced pigs lungs. It contains approximately 99% lipids, mainly phospholipids, and 1% low molecular weight hydrophobic apoproteins SP-B and SP-C.[14] Infants were randomly assigned to receive either 1·25 or 2·5 ml/kg body weight (100 mg or 200 mg/kg) with the aim of achieving rapid distribution throughout the lung. Half was delivered into each main bronchus by positioning the infant on one side before instilling the surfactant intratracheally and continuing mechanical ventilation in that position for one minute. The procedure was then repeated on the opposite side. Exosurf is a synthetic surfactant which contains 13·5 mg/ml of dipalmitoyl phosphatidyl choline, 1·5 mg/ml cetyl alcohol, 1 mg/ml tyloxapol in 0·1 N sodium chloride and no surfactant apoproteins.[2] Over approximately 20–30 minutes 5 ml/kg was administered into the proximal endotracheal tube. The infants remained supine and mechanical ventilation continued throughout. Exosurf was

administered more slowly than Curosurf to reduce the risk of poorer tolerance of the larger volume.

Oxygenation, ventilator efficiency index (VEI), and static Crs were assessed in each infant shortly before and as close as possible to three and 12 hours after the first dose of surfactant. All the infants were ventilated with Sechrist IV 100b pressure limited, time cycled, continuous flow ventilators. The investigators were not responsible for the clinical care of the infants. The study was accepted by the ethical committees of both hospitals. Written informed consent was obtained from one or both parents before including their infant in the study.

STATIC CRS MEASUREMENTS

Static Crs was measured using a computerised passive expiratory flow technique as previously described,[15] using software developed at the Children's Hospital, Toronto by Professor A C Bryan, Dr M H Bryan, and Dr P N Le Souef. To standardise for body size, Crs values were corrected for body length because we had found this slightly more accurate than correction for weight in predicting both hospital death and an immature lung phospholipid profile.[15 16] All Crs results were calculated as the mean of 3–6 satisfactory breaths. Breaths were only accepted if there was a clearly defined pressure plateau (approximately 200 msec) after airway occlusion, if the linear portion of the expiratory flow-volume curve accounted for two thirds or more of the expiration, and if the correlation coefficient for the slope of the asymptote to the flow-volume curve was >0·996. Studies were only accepted if they had a within-study coefficient of variation between breaths of <15% and no study required exclusion on this criterion. In comparing sequential studies on the same infant we planned to conduct them all within a range of expired volume of 5–10 ml/kg body weight. Occasionally the expired volume was less than this in infants with very stiff lungs. None of these results was excluded, as subsequent studies in these infants were conducted at similar pressures or expired volumes. Changes in Crs were expressed as percentage differences of the pretreatment value. We planned before analysis to subdivide the infants according to whether or not their static Crs before treatment was consistent with surfactant deficiency (<1·8 ml/cm H_2O/m).[16]

OXYGENATION

Arterial oxygen tension (Pa_{O_2}) was measured intermittently by blood gas analysis. Oxygenation was expressed as the fractional inspired oxygen (F_{IO_2}) required at the time of study to maintain the infants' arterial or continuously monitored transcutaneous oxygen tension between 6 and 10·3 kPa or their oxygen saturation between 90 and 94% by continuous pulse oximetry. Transcutaneous oxygen tension was calibrated against Pa_{O_2} by intermittent arterial puncture.

VENTILATOR REQUIREMENTS

In order to adjust for variations in ventilator settings between infants, we used the VEI devised by Notter *et al.*[17] This index estimates alveolar ventilation in relation to ventilator settings and can be calculated by the equation:

$$VEI = \frac{3800}{p \times f \times Paco_2}$$

where p is the inspiratory pressure minus the expiratory pressure of the ventilator, f is the ventilator rate in cycles per minute, and $Paco_2$ is the arterial carbon dioxide tension in mm Hg. VEI increases rapidly as ventilation requirements become minimal. Therefore all VEI values of >1 were defined as 1 in the group comparisons.

STATISTICAL ANALYSIS

Results were analysed using SPSS-PC and Minitab. Variables were compared three and 12 hours after treatment with their corresponding pretreatment value in paired group analyses using the Wilcoxon matched pairs signed ranks test. Distributions of each variable were compared using the Mann-Whitney U test. A two tailed probability was accepted as statistically significant if $p<0·05$.

Results

During the study period 111 infants were treated with surfactant in the two centres. Of these the 88 who were enrolled in this study (table 1) did not differ significantly in important prognostic characteristics. Pairs of Crs measurements were made successfully in 73 of these 88 infants (83%). The reasons for failure to obtain Crs data in the others were (i) inability to obtain adequate pressure plateaux after airway occlusion (either because of air leaks around the endotracheal tube or failure to induce a Hering-Breuer reflex in active infants) or (ii) alinearity of the flow-volume relationship. Of the 15 infants without successful Crs measurements nine received Curosurf and six Exosurf. There were no statistically significant differences between them and the babies in whom Crs was measured successfully in birth weight, gestational age, or oxygen requirement before

Table 1 Infants eligible for study, enrolled and successfully measured. Gender, gestation, birth weight, and length by surfactant; data are expressed as median (range)

	Curosurf	*Exosurf*
Eligible	56	55
M/F	35/21	33/22
Gestation (weeks)	29 (23–37)	30 (23–38)
Birth weight (g)	1253 (580–3250)	1370 (600–4150)
Enrolled	48	40
M/F	31/17	26/14
Gestation (weeks)	29 (23–35)	29 (25–38)
Birth weight (g)	1226 (580–2540)	1285 (607–4150)
Measured	39	34
M/F	26/13	21/13
Gestation (weeks)	29 (25–35)	29 (25–38)
Birth weight (g)	1253 (677–2540)	1285 (607–4150)
Length (cm)	38 (32–49)	40 (33–52)

Table 2 Pretreatment patient characteristics by surfactant and initial Crs; data are expressed as median (range)

	Curosurf (<1·8 ml/cm H_2O/m) (n=32)	*Exosurf (<1·8 ml/cm H_2O/m) (n=26)*	*Curosurf (≥1·8 ml/cm H_2O/m) (n=7)*	*Exosurf (≥1·8 ml/cm H_2O/m) (n=8)*	*All (<1·8 ml/cm H_2O/m) (n=58)*	*All (≥1·8 ml/cm H_2O/m) (n=15)*
Gestation	28 (25–35)	29 (25–38)	32 (28–35)	35 (25–37)	28 (25–38)†	32 (25–37)†
Birth weight (g)	1159 (677–2540)	1240 (607–4150)	1690 (1263–2460)	2840 (703–3600)	1195 (607–4150)‡	2260 (703–3600)‡
Length (cm)	37 (32–47)	39 (33–52)	44 (37–49)	48 (34–51)	38 (32–52)‡	46 (34–51)‡
M/F	22/10	15/11	4/3	6/2	37/21	10/5
Age at first dose (decimal hour)	5·00 (2·35–37·2)	5·10 (3·15–50·8)	16·98 (3·63–53·5)	22·65 (5·13–41·32)	5·01 (2·35–50·8)†	16·98 (3·63–53·5)†
Initial Crs/m	1·1 (0·6–1·6)	1·1 (0·5–1·7)	2·1 (1·8–2·6)	2·1 (1·8–2·7)	1·1 (0·5–1·7)	2·1 (1·8–2·7)
Initial F_{IO_2}	0·68 (0·32–1·0)	0·73 (0·30–0·95)	0·60 (0·50–1·0)	0·63 (0·48–0·90)	0·70 (0·30–1·0)	0·60 (0·48–1·0)
Initial VEI	0·13 (0·05–0·43)*	0·12 (0·08–0·26)*	0·19 (0·11–0·64)	0·16 (0·09–1·0)	0·13 (0·05–0·43)*	0·19 (0·09–1·0)*

Symbols denote significant difference between groups (Mann-Whitney U).
*p = <0·05, †p = <0·005, ‡p = <0·0005.

treatment or in changes in oxygen requirements and VEI after treatment with either surfactant.

The mean (SD) within study coefficient of variation in Crs between accepted breaths in 134 sequentially analysed studies was 6·7 (3·5)%. The mean (SD) difference between the results of paired studies performed five minutes apart by the same observer on 15 infants >12 hours after treatment with surfactant was 0·2 (10·5)%. The mean (SD) difference between the results obtained by two different observers analysing the same data, blind to the results obtained by the other in 71 randomly selected studies was 0·4 (7·4)%.

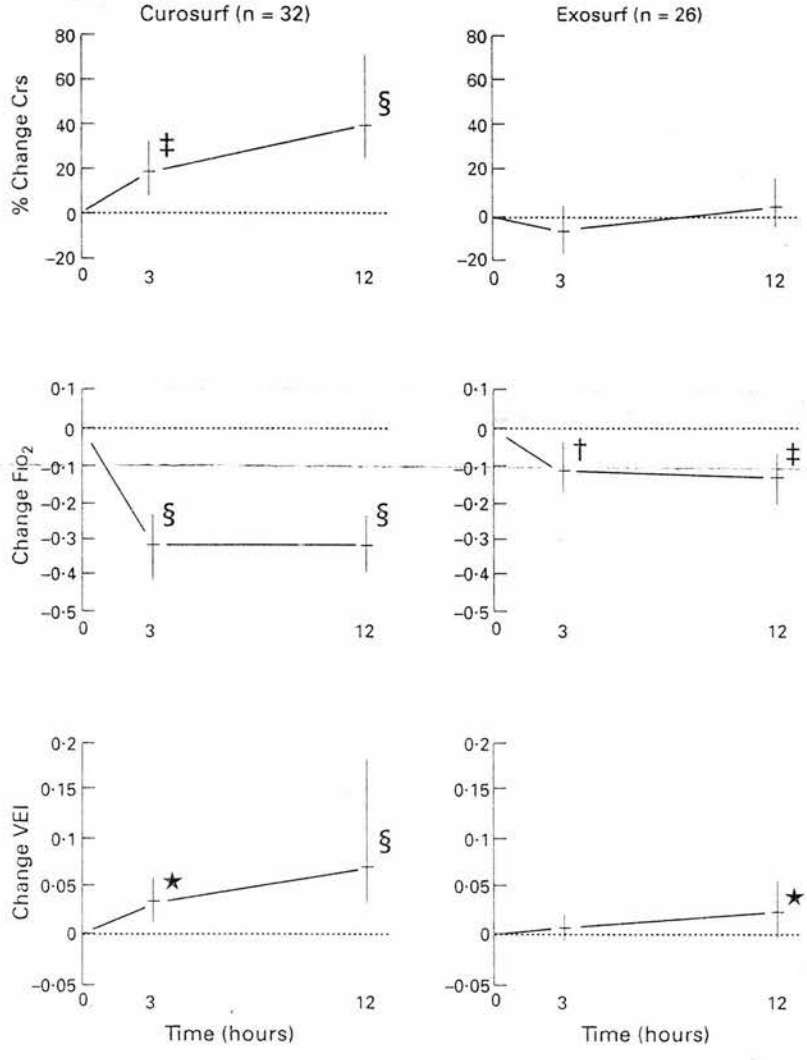

*Figure 1 Changes after surfactant administration in infants with initial Crs <1·8 ml/cm H_2O/m. Graphs show medians with 95% confidence intervals. Symbols denote significant difference from value before treatment: *p<0·05, †p<0·01, ‡p<0·005, §p=0·0001 by Wilcoxon signed rank test.*

Of the 73 infants with valid Crs data, there were no differences in the distributions of birth weight, length, gestational age, oxygen requirement, age at treatment, and static Crs before treatment between those treated with Curosurf and those treated with Exosurf (table 2). The infants with initial values of static Crs suggesting surfactant deficiency (<1·8 ml/cm H_2O/m) who received Exosurf had slightly greater ventilation requirements (VEI) before treatment than those treated with Curosurf. There were 15 infants whose static Crs before treatment was not consistent with surfactant deficiency (≥1·8 ml/cm H_2O/m). They were significantly heavier, longer, easier to ventilate, older at time of treatment, and of later gestation than those whose initial Crs was consistent with surfactant deficiency.

The changes in Crs, oxygen requirements, and VEI seen after treatment are shown in figs 1 and 2. Of the 58 infants with initial Crs <1·8 ml/cm H_2O/m (fig 1) those treated with Curosurf showed a median improvement in Crs of 18% (p=0·002) three hours after treatment increasing to 39% (p=0·0001) at 12 hours. These changes were accompanied by significant improvements in oxygenation and VEI at both three and 12 hours. The infants treated with Exosurf showed no statistically significant changes in Crs at three or 12 hours, with median changes of −6·2% (p=0·24) at three hours and +5% (p=0·28) at 12 hours. Their oxygen requirements were significantly lower at three hours than before treatment but the VEI did not improve until 12 hours. The median reduction in oxygen requirement was greater after Curosurf than Exosurf both at three hours (change in F_{IO_2} −0·32 compared with −0·11; p<0·001) and at 12 hours (change in F_{IO_2} −0·32 compared with −0·13; p<0·005) after treatment. If the Crs results for these infants are expressed in absolute terms rather than as percentage changes, the same pattern is observed with median pretreatment Crs for the Curosurf treated infants of 1·1 ml/cm H_2O/m and median change at three hours +0·2 (p=0·0037), and median pretreatment Crs for the Exosurf treated infants 1·1 ml/cm H_2O/m and median change at three hours −0·1 (p=0·156). At each time point in fig 1 the medians and 95% confidence intervals for each of the three variables were calculated from the same infants except that there was

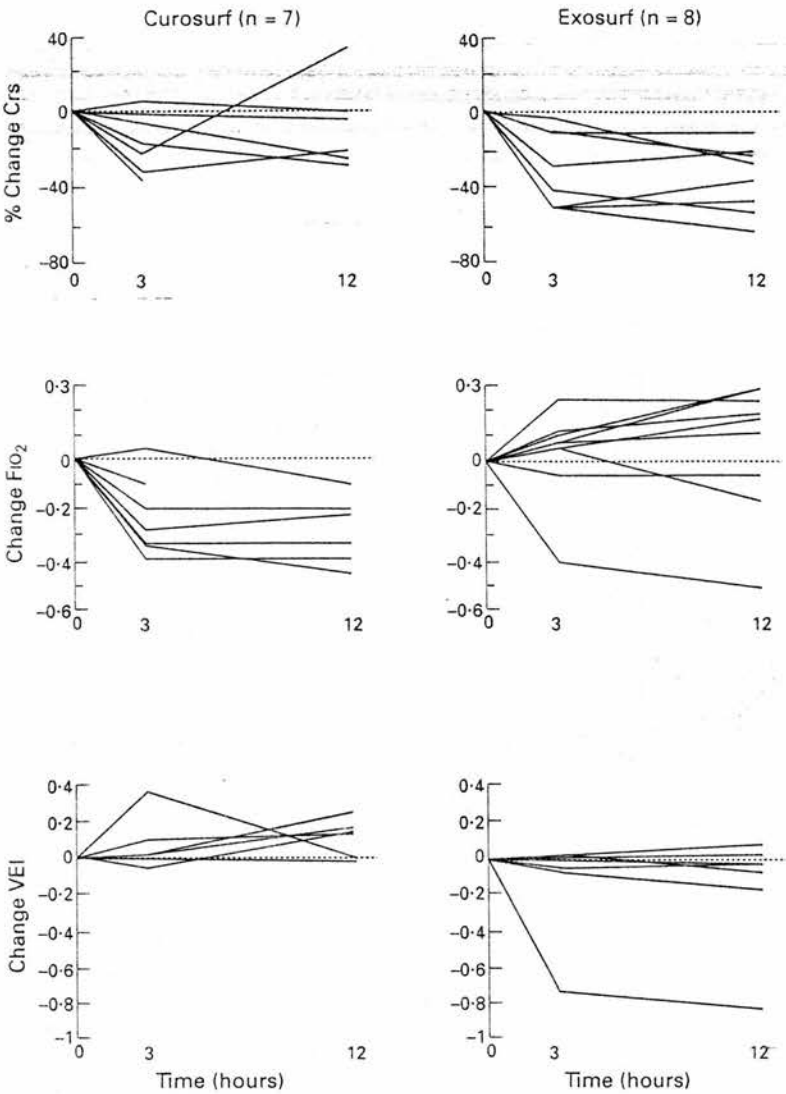

Figure 2 Changes after surfactant administration in infants with initial Crs ≥1·8 ml/cm H_2O/m. Lines represent individual infants.

one missing data point for the VEI in an infant treated with Exosurf.

Of the 15 infants with initial Crs ≥1·8 ml/cm H_2O/m (fig 2), all eight treated with Exosurf and five out of seven treated with Curosurf showed a fall in Crs after treatment. The infants treated with Curosurf showed an overall reduction in their oxygen requirements while those treated with Exosurf did not. There was no consistent pattern to the changes in the VEI.

Discussion

In this study infants diagnosed as respiratory distress syndrome with a/A ratio <0·22 showed rapid improvements in static Crs, oxygenation, and ventilation requirements after porcine surfactant if their initial static Crs was consistent with surfactant deficiency. A similar group of infants showed no improvement in static compliance, a smaller improvement in oxygenation, and no significant reduction in ventilation requirements over the same time after synthetic surfactant. It should be stressed that these two groups were not randomly assigned to natural or synthetic surfactant, so this comparison should be interpreted with caution. However, the results are consistent with individual studies of naturally derived[12] and synthetic surfactants[11] using the same methods in human infants and with randomised studies in animals.[4] Improved pulmonary pressure-volume characteristics are therefore likely to be an important factor in the rapid clinical improvements seen after natural surfactant.

Several clinical studies on ventilated human infants have failed to show rapid improvements in lung mechanics that would explain the immediate improvements in gas exchange seen after surfactant treatment.[5–11] Some of these studies involved infants treated with synthetic surfactant,[5 6 7 11] which may have slower effects on lung mechanics than natural surfactant. Three considered infants treated with natural surfactants, who showed rapid improvements in oxygenation but no concurrent improvements in dynamic compliance during ventilation.[8–10] The improvements in gas exchange have been attributed to documented improvements in functional residual capacity (FRC). These observations and conclusions may partly reflect the limitations inherent in measuring dynamic compliance. When positive end expiratory pressure is being applied to compliant lungs, they may remain sufficiently distended at end expiration to cause the lungs to operate higher up on the flatter part of the pressure volume curve during ventilator breaths. Under these circumstances there might be no net improvement in dynamic compliance but a large improvement in FRC and hence oxygenation. The passive expiratory flow technique for measuring static compliance avoids this problem by measuring expired volume from peak inflation to zero (atmospheric) pressure. This has recently been elegantly demonstrated by Kelly *et al* who measured compliance by both methods in a population of infants treated with a naturally derived surfactant and demonstrated significant improvements in static compliance without improvements in dynamic compliance.[12] If the lungs are operating on the flat upper portion of the pressure volume curve because of excessive peak inflation pressure, however, this would lead to underestimation of changes in both dynamic and static compliance. Indeed Kelly *et al* reported improvements in both static and dynamic compliance when peak inflation pressure was reduced after surfactant treatment.[12]

Infants in this study are unlikely to have been ventilated with excessive peak inflation pressure as their expired volumes, extrapolated to zero flow and atmospheric pressure, were 5–10 ml/kg body weight or less. Although static Crs in respiratory distress syndrome improved after treatment and oxygen requirements often decreased substantially in this study the infants still required to be ventilated, often vigorously, and their respiratory compliance did not reach the levels seen in infants without lung disease. Surfactant therefore alleviated but did not cure their respiratory distress syndrome.[12]

Part of the difference in the speed of response that we observed between the two surfactants in our study may reflect differences

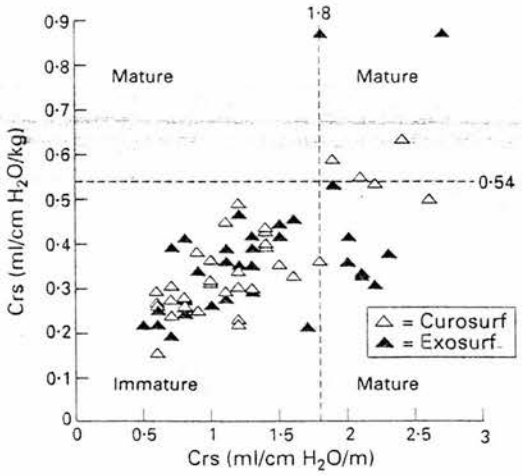

Figure 3 Crs corrected to weight (kg) in relation to Crs corrected to length (m).

in the methods of surfactant administration. Nevertheless, rapid response to a surfactant may not lead to improvements in adverse clinical outcome. In the Curosurf 4 trial for example, oxygenation and ventilation requirements improved faster in infants given an initial dose of 200 mg/kg of surfactant than in those given 100 mg/kg but there was no clear difference in mortality or major morbidity between them.[13]

The observations that in 15/73 (21%) of the infants static Crs was consistent with mature lungs (≥1·8 ml/cm H_2O/m[16]) before surfactant treatment and that in 13 of them static Crs fell after treatment raise important questions. Should they have received surfactant? Did it do more harm than good? Are clinicians being tempted to overdiagnose respiratory distress syndrome now that an effective treatment is available?[18–20] These 15 infants may have had respiratory problems other than respiratory distress syndrome, which can be difficult to discriminate on an early chest radiograph. If so, the apparently poorer lung mechanics and gas exchange of the eight 'mature' infants after Exosurf may have reflected the adverse effects of the greater volume of fluid instilled into their lungs. The seven mature infants treated with Curosurf still showed a reduction in their oxygen requirements, which might reflect more rapid clearance of administered fluid and continuing improvement in their underlying condition. Larger numbers are required to validate these observations.

Should static Crs be corrected for length or for weight? The lack of improvement in static Crs after surfactant treatment in 13 infants classified as mature (with static Crs ≥1·8 ml/cm H_2O/m) seems consistent with the behaviour of mature lungs. However, had we instead corrected static Crs for weight using a predefined cut off for lung maturity of ≥0·54 ml/cm H_2O/kg based on previous work,[16] only five infants would have been identified as having mature lungs (fig 3). Furthermore, six out of the eight infants treated with Exosurf whose lung mechanics and gas exchange did not improve would have been identified as immature, which seems inconsistent with their lack of response to surfactant.

This supports the suggestion that correction of static Crs for weight may slightly overestimate the disease severity of larger infants relative to smaller ones.[15] In this and two other studies therefore,[15 16] correction of static Crs for length appears to have been more informative than correction for weight. This may be important in planning future studies. Nevertheless until reliable data from randomised trials are available, we would urge caution in giving or withholding surfactant on the basis of a single lung function test.

In summary, this study describes early responses to treatment with two surfactants. The results do not provide definitive evidence in favour of either. There may be moderate but important differences in major clinical outcomes between natural and synthetic surfactants, but to demonstrate them reliably would require international collaboration. For example, a sample of 4000 would be needed to detect a reduction in the risk of death or bronchopulmonary dysplasia in high risk infants from 67% to 62% with 90% power at 2p=0·05.[21] Respiratory distress syndrome remains a common and disabling condition. Detecting differences of this magnitude is logical and feasible[18] and poses a worthwhile challenge to the international community.

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LIFE-THREATENING INADVERTENT POSITIVE END-EXPIRATORY PRESSURE

Ben J. Stenson, M.R.C.P., Rebecca M. Glover, M.R.A.C.P., Rosalie A. Wilkie, F.R.C.P.E., Ian A. Laing, F.R.C.P.E., and William O. Tarnow-Mordi, M.R.C.P.

ABSTRACT

Inadvertent positive end-expiratory pressure (PEEP) is a potential cause of lung overdistension and impaired gas exchange in ventilated infants. It can be extremely difficult to diagnose clinically and if unrecognized can be life-threatening. Measurement of lung function can lead to the recognition of inadvertent PEEP, allowing appropriate ventilator adjustment with immediate substantial improvement in clinical state. Lung function measurements can help to optimize ventilation and may improve clinical outcome.

Keywords: Positive end-expiratory pressure; gas exchange; lung distension; ventilation

During mechanical ventilation, when lung inflation occurs before the preceding deflation is completed, gas is trapped in the lungs. The trapped gas increases the lung volume and exerts a positive pressure within the airspaces, which is not apparent clinically. The phenomenon is called inadvertent positive end-expiratory pressure (PEEP).[1,2] Respiratory dead space increases, impairing gas exchange. Tidal volume decreases because the effective difference between the inspiratory and expiratory pressures is reduced. Cardiac output may be impaired by the increase in intrathoracic pressure.[3]

Passive expiration occurs exponentially and the time required is determined by the expiratory time constant.[4] This is the mathematical product of the compliance and resistance of the respiratory system. The time constant describes the time taken for 63% of the lung volume above functional residual capacity to be passively exhaled. After three time constants, expiration is 95% complete and clinically important gas trapping is unlikely. Increases in compliance or resistance lengthen the time constant and thereby prolong the time required for efficient expiration. Long expiration times are especially likely to be required where compliance is not severely impaired but airway resistance is high, as may be the case in chronic lung disease.

Lung function can be measured in ventilated infants using the single breath passive expiratory flow technique.[5,6] An airway occlusion during inspiration is used to induce a Hering-Breuer reflex. This briefly inhibits the respiratory muscles and during the pause in respiratory activity the infant is allowed to exhale passively to atmospheric pressure. The characteristics of the relaxed expiration are used to calculate the compliance, resistance, and time constant of the respiratory system.

Inadvertent PEEP can be extremely difficult to diagnose clinically. We report on three infants in whom it was life-threatening. Lung function testing aided its recognition and a change of ventilation led to a dramatic clinical improvement.

CASE REPORTS

Case 1

A male infant was delivered at 25 weeks' gestation with birthweight of 890 g. He required ventilation and remained ventilator dependent. On day 26, his respiratory function deteriorated. The chest radiograph showed bilateral hazy opacification and he was treated with antibiotics. By day 32, his ventilator settings had gradually increased to 50 breaths per minute, with inspired oxygen concentration 60%, and he was started on dexamethasone. Over the next 3 days, he deteriorated further. His oxygen requirements rose to 90% and the ventilator rate was increased to 60 breaths per minute with pressures 24/5 cm H_2O and inspiration time was 0.45 seconds. The infant was critically ill and hypoxic. He was reintubated without improvement. Lung function measurements were obtained (Fig. 1). Respiratory system compliance was 3.2 mL/cm H_2O/m body length (1.0 mL/cm H_2O/kg) which is within the normal range. The time constant was 0.26 seconds, giving a time for 95% exhalation of 0.78 seconds (3 time constants). The ventila-

Department of Child Life and Health, University of Edinburgh, and Department of Child Health, Centre for Research into Human Development, Ninewells Hospital and Medical School, Dundee, Scotland, United Kingdom

Reprint requests: Dr. Stenson, Lecturer in Paediatrics, Neonatal Unit, Simpson Memorial Maternity Pavilion, Edinburgh, Scotland, UK

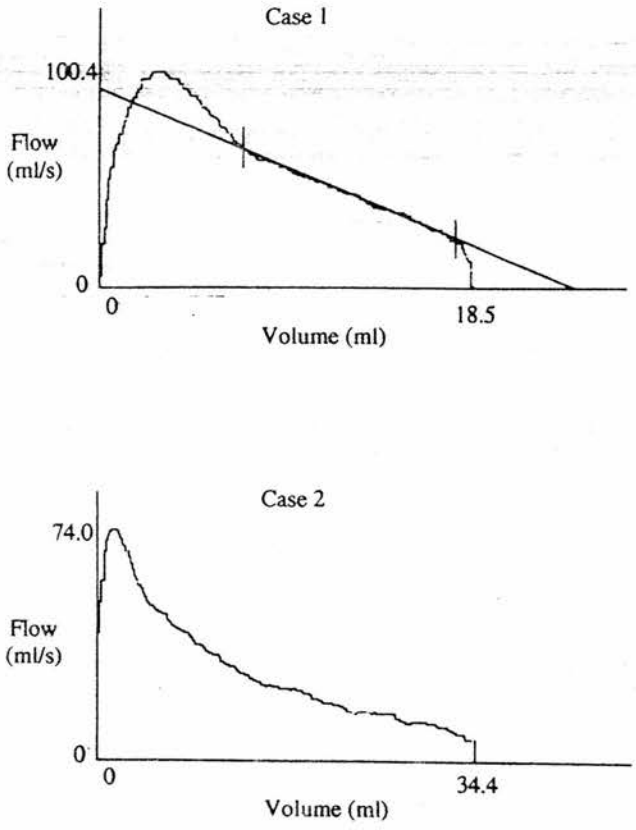

Figure 1. Passive expiratory flow-volume curves. The slope of the straight line extrapolated to the axes in case 1 is equal to the time constant of the respiratory system.

tor settings allowed 0.55 seconds. The expired volume was 14.4 mL/kg body weight (normal tidal volume is 7 to 9 mL/kg[7]). These findings indicated gas trapping and inadvertent PEEP. The ventilator rate was reduced to 40 breaths per minute and the pressures to 16/4 cm H_2O with inspiration time of 0.45 seconds. The infant's oxygen requirements fell immediately to 50% with no increase in arterial partial carbon dioxide pressure (PCO_2) and over the next 18 hours continued to fall to 25%. The infant was extubated into head-box oxygen 3 days later.

Case 2

A male infant was delivered at 27 weeks' gestation with birthweight of 1089 g. He received surfactant for respiratory distress syndrome and was extubated on day 10. On day 30, he deteriorated with recurrent apnea and increasing oxygen requirements. The chest radiograph showed bilateral patchy consolidation. He was ventilated and stabilized on ventilator settings of 20 breaths/min, pressures 22/4 cm H_2O, and 30% oxygen. The next day he became increasingly difficult to ventilate. Neither fast nor slow rate approaches prevented him from deteriorating and requiring manual ventilation.

Arterial blood gases showed pH 6.9; PCO_2, 138 mm Hg; partial oxygen pressure (PO_2) 59 mm Hg; base excess, −8.2 mmol/L. He was reintubated without improvement. Later that day, it was only possible to maintain gas exchange by manual ventilation with 100% oxygen and he was handbagged for more than an hour. Passive respiratory mechanics could not be calculated because the flow volume trace was very irregular (Fig. 1), but the expiratory flow-time trace (Fig. 2) showed extremely prolonged expiration. The expired volume was 23 mL/kg, indicating marked overinflation. The infant was paralyzed and the ventilator set at 20 breaths per minute, pressures 25/4 cm H_2O, inspiration time 0.6 seconds. His condition stabilized immediately. It was now easy to see the prolonged expiratory phase and an obvious wheeze was audible that had not been detectable earlier. Four hours later, the arterial PCO_2 had fallen to 23 mm Hg and the inspired oxygen concentration was 52%. The presumed cause of deterioration was infection, but this was not proven. The infant remained on low rate ventilation with low oxygen requirements and was extubated on day 53.

Case 3

A male infant was delivered at 27 weeks' gestation with birthweight 750 g. He had no early lung disease and was extubated on day 1. On day 5, his respiratory function deteriorated. The chest radiograph showed bilateral hazy opacification. He was treated with antibiotics and was ventilated with low rate pressures and oxygen concentration. By day 10, the chest radiograph showed a honeycomb appearance bilaterally. He continued to deteriorate and on day 14 dexamethasone was started. There was no significant improvement and from days 14 to 19 he required more than 90% oxygen. By this time, the ventilator settings had increased to 55 breaths per minute, pressures 24/4 cm H_2O, inspiration time 0.5 seconds, and 100% oxygen. Reintubation made no difference. Arterial blood gases showed pH 7.39; PCO_2, 38 mm Hg; and PO_2, 55 mm Hg. There was no clinical improvement with nebulized ipratropium bromide.

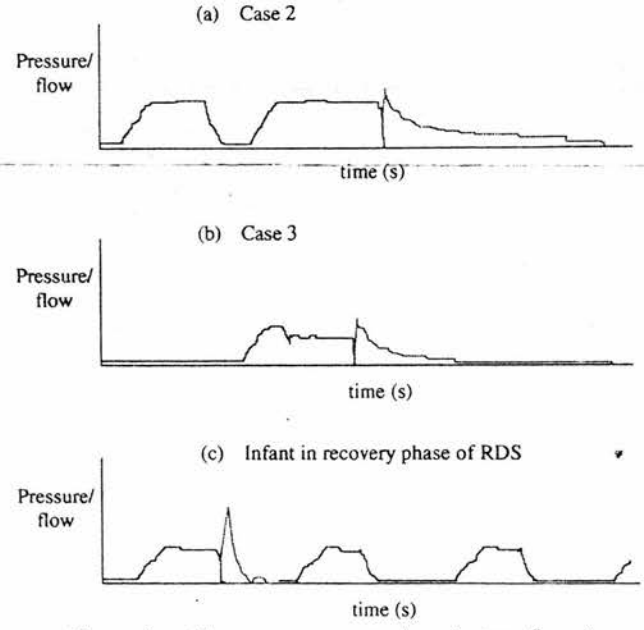

Figure 2. Airway pressure- and expiratory flow-time. Cases 2 and 3 with tracing from an infant recovering from RDS for comparison. — Proximal airway pressure during ventilation. Recording stops when ventilation is interrupted to sample passive expiratory flow. ····· Passive expiratory flow from peak inflation to atmospheric pressure.

Because of his respiratory efforts, lung function measurements were impossible until he was paralyzed.

The expiratory flow-time trace showed markedly prolonged expiration (Fig. 2) and the volume expired to atmospheric pressure was 17.5 mL/kg, indicating gas trapping. The infant was ventilated at 25 breaths per minute with pressures 24/4 cm H_2O and inspiration time of 0.6 seconds. His oxygen requirements fell rapidly and were 30% 5 hours later, with a minimal increase in arterial PCO_2. Pancuronium was discontinued after 3 days and the infant was extubated on day 37.

DISCUSSION

Inadvertent PEEP is often detectable in ventilated infants if measurements are made,[2] but the degree of clinical importance attached to it is variable.[8] Such severe clinical problems in relation to it have not been reported in the newborn. The airway obstruction common in chronic lung disease makes inadvertent PEEP especially likely to occur but any cause of increased airway resistance such as a kinked or blocked endotracheal tube or reactive airways can lengthen the time required for expiration and potentially result in inadvertent PEEP. In the three cases described the problems evolved gradually and the ventilator rates had been increased slowly in response to respiratory acidosis, which developed at lower rates. Chest hyperinflation was not apparent clinically or radiologically. Chest movement with the ventilator was poor and expiration did not appear prolonged. This may have been because gas trapping can force tidal volume exchange to occur further up the lung pressure-volume curve in its flatter portion where compliance is reduced and resistance may also be lower.[2,9] This would tend to make the early part of expiration appear rapid. Under these circumstances, expiration during the time allowed by the ventilator settings may not appear prolonged and this may only become apparent if ventilation is interrupted to allow complete expiration. Even then, the infant's own respiratory efforts may still confuse the issue. In case 2, low rates were tried without improvement and it was only when they were imposed by the addition of pancuronium that success was achieved. It is possible that in cases 2 and 3 asynchronous ventilation was contributing to the problem. Both infants were given pancuronium. However, lung function testing indicated lung overdistension and a prolonged expiratory phase and gas exchange improved markedly when the ventilator rate was slowed.

Simbruner[2] demonstrated improved respiratory system compliance using a fixed tidal volume when inadvertent PEEP was decreased. He measured the compliance at the lung volume immediately above that generated by the inadvertent PEEP. He concluded that reducing the overdistension had allowed the lung to operate in a more efficient region of the pressure-volume relationship. This finding would not be demonstrable using the single breath technique as it allows complete exhalation to atmospheric pressure and therefore the trapped gas that is generating the inadvertent PEEP is also exhaled.

The single breath passive expiratory flow technique may allow measurement of the time constant and facilitate adjustment of the expiration time to avoid inadvertent PEEP, but it is often not applicable in infants with severe chronic lung disease. The technique requires the passive expiratory flow-volume trace to be linear over the expired volume range. In cases 2 and 3 this was not so. The trace in case 1 (Fig. 1) was predominantly but not completely linear. There is no clear consensus as to exactly what proportion of the trace needs to be linear for this technique to be used. In addition, the placement of a straight line over the flow-volume trace is subjective and allows some small variation in the values obtained.

Despite the difficulty of applying the single breath technique in full in two of these infants, the apparatus supplied important information that allowed effective ventilator adjustments that were followed by marked clinical improvements. Our experiences suggest that potentially life-threatening inadvertent PEEP may frequently remain unrecognized. Crib-side measurements of lung function may improve the management of ventilated infants.

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B. J. Stenson
R. A. Wilkie
I. A. Laing
W. O. Tarnow-Mordi

Reliability of clinical assessments of respiratory system compliance (Crs) made by junior doctors

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B. J. Stenson (✉) · I. A. Laing
Neonatal Unit, Simpson Memorial Maternity Pavilion, Edinburgh EH3 9EF, UK

R. A. Wilkie · W. O. Tarnow-Mordi
Ninewells Hospital and Medical School, Dundee, UK

Abstract *Objective:* To assess the reliability of estimates of static respiratory system compliance (Crs) made by junior hospital doctors caring for ventilated newborn infants.
Design: A prospective comparison of junior doctors' estimates of Crs to the Crs measured immediately afterwards.
Setting: A regional neonatal intensive care nursery in Edinburgh, Scotland.
Patients: 46 ventilated newborn infants.
Measurements and results: Crs was estimated by three grades of junior doctor (Senior House Officer, Registrar and Research Fellow) using two different methods, (i) based on visual assessment of tidal volume in relation to inflation pressure (optical Crs) and (ii) directly using a visual analogue scale (analogue Crs). The Crs was then measured immediately afterwards using the single breath passive expiratory flow technique. The differences between the estimates and the measurements were calculated for each grade of observer and plotted against the corresponding measurements. The relationship between estimates and measurements was also expressed in terms of the coefficients of determination r^2 calculated by least squares regression. With both methods of estimation observers tended to overestimate the Crs of infants with lower measured Crs and underestimate that of infants with higher measured Crs with many estimates differing from the measurements by more than 50%. Values of r^2 ranged from 0.086 to 0.481 indicating a weak relationship between the estimates and the measurements.
Conclusions: Junior doctors' estimates of Crs were unreliable and did not represent a useful method of assessing respiratory function. The clinical use of compliance measurements merits wider evaluation.

Key words Pulmonary function testing · Lung compliance

Introduction

Whenever an infant is mechanically ventilated the person adjusting the ventilator makes an informal appraisal of the lung mechanics by visually estimating the chest inflation. Estimates of static respiratory system compliance (Crs) based on clinical assessment of chest inflation have been proposed as a useful aid to ventilator management in neonatal intensive care [1, 2]. The reliability of clinical judgements is likely to vary with clinical experience and estimates made by the junior doctors who provide much of the care to ventilated infants may be less reliable than those of their seniors. It can be difficult to make an accurate diagnosis from a chest radiograph [3]. Blood gas analysis measures the effect of the current ventilator set-

tings rather than what they might ideally be and over-ventilation can substantially worsen gas exchange [4]. Given the subjective nature of the clinical information available, objective lung function data such as Crs measurements might help to optimise ventilation strategy. But if junior doctors could reliably judge Crs then the additional infant handling and equipment costs associated with the measurements however minimal would be hard to justify. This study was designed to determine whether the junior doctors in a regional neonatal intensive care unit can make reliable clinical estimates of static respiratory system compliance.

Materials and methods

A total of 46 ventilated newborn infants were studied prospectively in the Simpson Memorial Maternity Pavilion, Edinburgh between September 1992 and June 1993. Infants were eligible for inclusion if on the first day of life the Senior House Officer (SHO), Registrar and Research Fellow were simultaneously available to estimate Crs and no preceding Crs measurements had been made. Written parental consent was obtained in all cases. The study was conducted according to the principles established in Helsinki and with the approval of the local ethics committee. Crs was estimated using two methods and the estimates were compared to the measured Crs obtained immediately afterwards.

Crs estimates

The methods of estimation were: (a) optical Crs, and (b) analogue Crs. Optical Crs is based on assessment of tidal volume [1, 2]. The examiner placed the chest inflation observed with each ventilator breath into one of three categories: less than normal and barely visible, approximately normal, or greater than normal and distinctly visible (normal being that observed in a healthy newborn infant breathing spontaneously). A tidal volume of 5, 7.5, or 10 ml/kg body weight was assigned accordingly. The values obtained were divided by the inflation pressure (peak inspiratory pressure minus positive end-expiratory pressure) to give the optical compliance (units ml/cmH_2O/kg body weight). Analogue compliance was estimated by marking a point on a linear scale corresponding to what the observer thought the Crs would be (Fig. 1). The scale described Crs values ranging from 0.4 (severely abnormal) to 2.5 ml/cmH_2O/m body length (functionally normal). Crs values were expressed on the analogue scale in relation to body length as Crs is routinely corrected for length in our unit [4–6]. In our experience infants recovering from lung disease can usually be extubated and are often breathing air by the time their Crs has reached 2.5 ml/cmH_2O/m but newborn infants with entirely normal lungs have a Crs of around 5–8 ml/cmH_2O/m [7–10] or 1–1.6 ml/cmH_2O/kg [11]. The optical estimates and measurements were compared to one another using their actual values. For the purposes of comparison to the analogue scale all measured Crs values that were greater than 2.5 ml/cmH_2O/m were called 2.5. Each observer was blind to the estimates made by the others.

0.6 Or less* (very stiff lungs) — 1.8 Or more § (minimal or no lung stiffness)

Fig. 1 Analogue scale for estimating Crs. *Crs ≤ 0.6 ml/cmH_2O/m means high risk of death from lung disease [4]. § Crs ≥ 1.8 ml/cmH_2O/m implies normal lung phospholipid profile [5]

Crs measurements

Immediately following the estimates, Crs was measured by the research fellow (BJS) using the single breath passive expiratory flow technique as previously described [4–6, 12]. This was then divided by the infant's crown-heel length measured with a tape measure (±1.5 cm) or birth weight in kg for comparison to the estimates.

Statistical methods

The difference between each Crs measurement and the corresponding Crs estimate was calculated (measurement minus estimate) and plotted against the measurement. In addition, the relationship between the estimates and measurements was assessed by the coefficients of determination (r^2) calculated from least squares regression. Statistical calculations were made by computer using Statview II.

Results

Complete data were obtained from 46 infants. Their characteristics are described in Table 1.

Figures 2 and 3 show the differences between each measurement and the corresponding estimates plotted against the measurements. The observations of all 3 grades of examiner are combined in each plot as the patterns were similar between observers. Both methods of estimation produced a similar distribution of observations with a tendency for examiners to overestimate the compliance of the infants with the lowest measured compliance and underestimate the compliance of the infants with the highest measured compliance. The estimates often differed by considerably more than 50% of the measured compliance. Table 2 shows the coefficients of determination (r^2) of the relationships between the measurements and estimates for each grade of examiner and each method of estimation. In all cases the measurements and estimates were only weakly related with r^2 values ranging from 0.086–0.481. Of the 46 infants, 6 (13%) had measured Crs values > 2.5 ml/cmH_2O/m. The values were 2.6, 2.8, 3.3, 3.5, 5.4, and 7.9.

Table 1 Patient characteristics expressed as median (range)

n	46
Gestational age (weeks)	31 (25–41)
Birth weight (kg)	1.496 (0.533–4.050)
Length (cm)	40 (29–57)
Crs (ml/cmH_2O)	0.518 (0.191–3.782)
Crs (ml/cmH_2O/kg)	0.358 (0.188–1.15)
Crs (ml/cmH_2O/m)	1.3 (0.5–7.9)

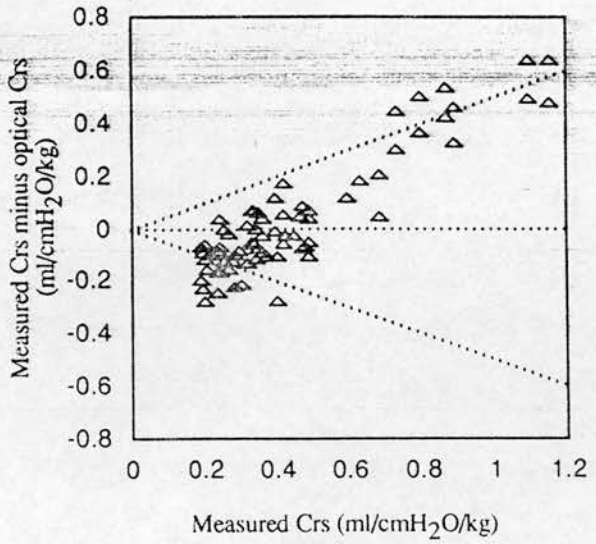

Fig. 2 Difference between measured and optical Crs. *Dotted diagonal lines* denote ±50% of the measured Crs

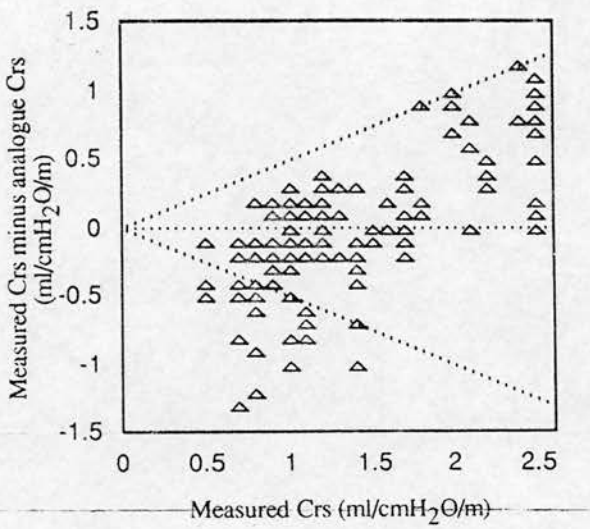

Fig. 3 Difference between measured and analogue Crs. *Dotted diagonal lines* denote ±50% of the measured Crs

Table 2 Relationship between optical or analogue estimates and measurements of static respiratory system compliance. The coefficients of determination (r^2) from least squares regression analysis are shown

Observer	Measured and optical Crs	Measured and analogue Crs
SHO	$r^2 = 0.086$	$r^2 = 0.400$
Registrar	$r^2 = 0.184$	$r^2 = 0.194$
Research fellow	$r^2 = 0.254$	$r^2 = 0.481$

Discussion

In this study junior doctors' estimates of static respiratory system compliance were unreliable. Neither method of estimating Crs performed within sufficient limits of accuracy to represent a realistic alternative to direct measurement.

The single breath passive expiratory flow technique for measuring Crs has been used in ventilated infants by many investigators and the Crs values in this study fell within the published ranges of diseased and normal infants. Although the scatter plots suggest that neither method for estimating Crs was clearly superior the r^2 values favoured the analogue estimates. This may be largely attributable to the upper limit of the analogue scale being at a Crs of 2.5 ml/cmH_2O/m. By assigning a value of 2.5 to the six measured Crs values above 2.5, inaccuracies that may have occurred over a wider range were avoided. If the results are reanalysed excluding these 6 datapoints the r^2 values are much closer to those of the optical estimates (SHO $r^2 = 0.342$, Registrar $r^2 = 0.081$, Research Fellow $r^2 = 0.267$).

The two other studies in the literature examining the abilities of doctors to estimate compliance [1, 2] concluded that estimates of optical compliance were closely correlated with measured compliance and may therefore be clinically useful. Both studies used correlation coefficients to describe the relationship between the measurements and estimates and neither expressed the Crs values in relation to the size of the infants. The second study also used the mean difference between the estimates and measurements plus or minus one standard deviation as a measure of agreement. Of the 45 data points in that study 15 fell outside those limits (as would be expected). Of the differences between the estimates and measurements 95% should lie between the mean difference ±2 standard deviations. These limits would have been approximately −55% to +41%. The estimates were made by a senior neonatologist and the limits of agreement were considerably narrower than those achieved by the junior doctors in this study but they are still quite wide.

Expression of compliance values in relation to infant size is important for two reasons. Firstly, in normal individuals compliance is proportional to lung and body size so large infants have a higher compliance than small infants. Only by expressing the compliance values in relation to infant size do they truly become a comparative measure of disease severity. Many investigators correct compliance measurements to body weight. We have found in other studies in this age group that correction to body length may be of marginally greater predictive value [4–6], hence the development of the analogue scale corrected for length. Secondly the correlation coefficient between two variables will improve as the range of observations widens [13]. Compliance values are spread over a much wider range if they are not expressed in relation to

body size. If the optical estimates and measurements in this study were considered without correcting them for body weight the range of observations would have been more than 3 times as broad and the r^2 values would have been 0.491 (SHO), 0.587 (Registrar) and 0.572 (Research Fellow). The ranges of observations for the Crs measurements corrected to body length (0.5–2.5, i.e. five fold) and weight (0.188–1.15, i.e. six fold) were similar.

The trend for the compliance of the sickest infants to be overestimated and of the healthiest infants to be underestimated by both methods is a reflection of the tendency of the observers to select values in the middle of the range in the majority of infants. 105/138 (76%) of the optical estimates were for the middle tidal volume option and the standard deviation of the analogue estimates was considerably narrower than that of the compliance measurements. This was also the finding of Aufricht et al. in an inexperienced observer [2]. If the poor reliability of the estimates is due to lack of clinical expertise or confidence it is difficult to speculate on ways of improving the methods of estimation to overcome this.

The measured Crs may not be the gold standard. The more important question is what gives the best indication of disease severity and is most useful in clinical practice. It should be stressed that there is as yet no data which clearly demonstrates that Crs measurements can improve the outcome of neonatal intensive care. In 1982 Crs measurements were found to measure reliably disease severity and predict outcome [14]. Another study has confirmed these findings although the Crs value associated with a high risk of death has lowered with time. This study also suggested that Crs may be a better measure of disease severity in ventilated infants than oxygen requirements [4]. Crs measurements can identify biochemical lung immaturity [5] and measure the response to surfactant treatment [6, 15]. They have been used to measure the effects of bronchodilators [16] and may identify infants suitable for extubation [17]. Automated systems for measuring pulmonary function are becoming increasingly available. If Crs measurement is to become more widely used to assist clinical management then substantial evidence that it can improve clinical outcome is required. This should be properly assessed in the context of a randomised controlled trial.

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